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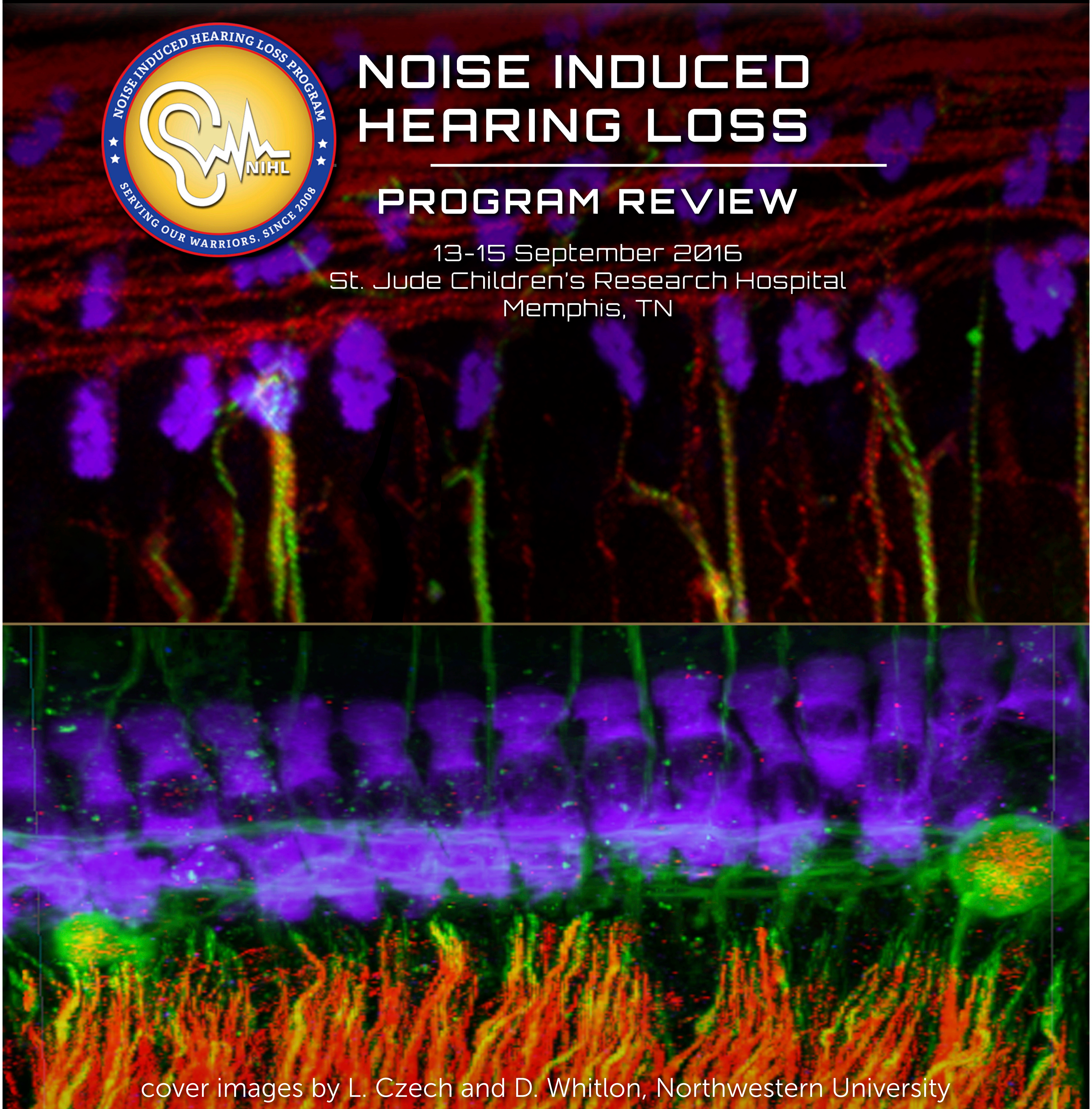

NOISE INDUCED HEARING LOSS PROGRAM
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NOISE INDUCED HEARING LOSS

PROGRAM REVIEW

13-15 September 2016
St. Jude Children's Research Hospital
Memphis, TN

cover images by L. Czech and D. Whitlon, Northwestern University

Abstracts

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DEPARTMENT OF DEFENSE
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Office of Naval Research
Noise-Induced Hearing Loss Program Review
13-15 September 2016
St. Jude Children's Research Hospital, Memphis, TN

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Status: New

TARGETING ATTENTIONAL MECHANISMS IN TINNITUS: CONTRIBUTION OF THE THALAMIC CHOLINERGIC SYSTEM

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Background

Tinnitus is defined as a phantom sound (ringing in the ears) that can significantly affect the quality of life for those experiencing it. There is a well-established link between high-level sound exposure and tinnitus, with soldiers deployed to battle zones 52.5 times more likely to suffer auditory damage than those non-deployed (Helfer et al., 2004). The American Tinnitus Association reports that 60% of auditory injuries, including tinnitus, within the veteran population were the result of a blast-induced injury. There is growing awareness of the importance of maladaptive attention mechanisms in the clinical pathology of tinnitus. Individuals most disturbed by their tinnitus are those whose attention is bound to the sensation. Proposed experiments examine cholinergic attentional mechanisms in the auditory thalamus or medial geniculate body (MGB) using a sound-exposure rat model. The MGB is a key component in the brain's tinnitus network, situated to gate the tinnitus sensation to the auditory cortex and limbic structures. Proposed experiments will characterize the nature and role of nicotinic cholinergic receptors (nAChRs) in MGB. Cholinergic projections to MGB, from the pedunculopontine tegmental nucleus (PPTg) are thought to modulate arousal and attention. Recently, we found that increased bursting in MGB output neurons correlates with behavioral measures of tinnitus. Preliminary studies suggest tinnitus-related changes in the subunit makeup of nAChRs in MGB. **Hypothesis:** Our working hypothesis suggests, that a phantom sound, without a physical correlate, and with related emotional involvement, results in increased activation of the PPTg. Thus, circuits involved in novelty detection and limbic circuits, inform the PPTg to "pay attention," resulting in tinnitus-related maladaptive activation of PPTg and hence, nAChRs in MGB. Consistent with this hypothesis, preliminary patch-clamp studies show cholinergic activation of presynaptic nAChRs on excitatory terminals which can be blocked by an nAChR antagonist. Collectively preliminary studies suggest a role for nAChRs in MGB and in the pathology of tinnitus.

Objectives

1. Determine tinnitus-related changes in the makeup and pharmacology of heteromeric nAChRs at the level of the MGB. 2. Determine the ability of application of nAChR antagonists to normalize tinnitus-related changes seen in the discharge properties of MGB neurons in slice/patch-clamp recordings from tinnitus animals. 3. Determine the ability of systemic administration of nAChR antagonists to normalize tinnitus-related anomalies in the attentional behavior of animals with behavioral evidence of tinnitus

Methods

All experiments will use an established sound-exposure behavioral model of tinnitus. Groups include: Exposed with tinnitus, exposed without tinnitus, and unexposed controls. SA1A will use receptor binding, immunoprecipitation and immunohistochemistry. SA1B will address tinnitus-related changes in the physiology and pharmacology of MGB neurons using *in vitro* MGB brain-slice preparation. SA2 will use an operant attention task to compare tinnitus-related changes between tinnitus and non-tinnitus animals. Systemically administered nAChR related compounds will be tested for their ability to normalize hyper-attentive responses seen in tinnitus animals.

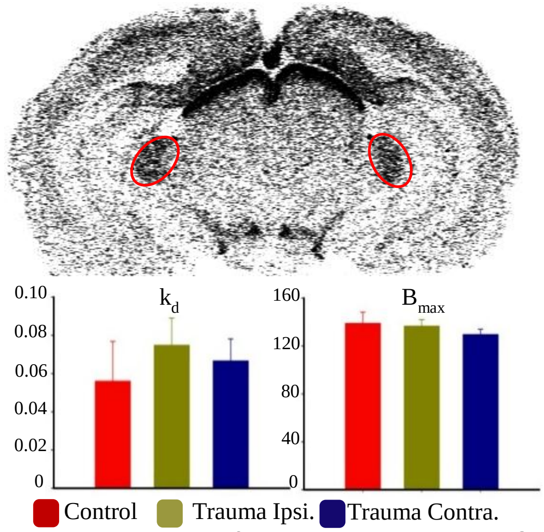

Fig.1. Autoradiogram of a cross-section through MGB, shows high levels of nAChRs ([3H]epibatidine 1.0nM) in the MGB (circled areas) from a control rat. Bottom: The trend toward the increase in Kd without a loss of nAChRs (Bmax) is suggestive of a subunit change in nAChR constructs.

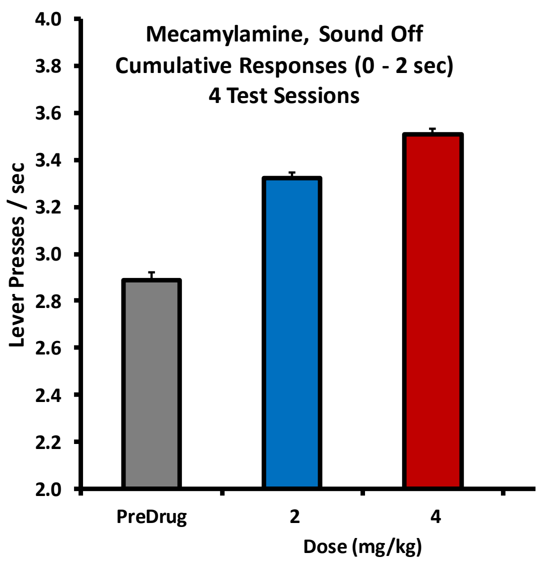

Fig. 2. Rats were trained in a vigilance task to stop lever pressing when a background sound randomly went silent. This vigilance response was attenuated with increasing doses of the nAChR antagonist mecamylamine. Higher numbers (lever presses) indicate decreased performance.

Results

Preliminary receptor binding results show high levels of binding for nAChRs in the MGB of control and sound exposed rats (Fig. 1). Preliminary tinnitus-related changes in nAChR affinity from autoradiographic studies underpin the planned competition binding studies (SA1). Binding studies will characterize the subunit makeup of nAChRs in the MGB of sound exposed animals with behavioral evidence of tinnitus using a number of pharmacologic approaches. It is likely that the magnitude of tinnitus distress relates to one's attention being fixed to this phantom auditory percept (Jacobson et al., 1996, Roberts et al., 2013). This could result in a decreased ability to focus ones attention on volitional activities.

Our preliminary behavioral studies found tinnitus-related differences in the ability of rats to attend (vigilance) to the random cessation of a background sound. In our rat model, auditory attention/vigilance was initially somewhat elevated in tinnitus animals. This attentional response was less responsive to environmental influence/training in animals with behavioral evidence of tinnitus. Performance on this attention task is thought to be, at least partially dependent on nAChR activation. When systemically treated with the non-selective nAChR antagonist, mecamylamine, increasing doses decreased vigilance, resulting in slower responses to the random cessation of the background sound (Fig. 2). In the coming year we will complete refinement of a complementary auditory selective attention task and begin testing for tinnitus-related changes in this feature of attention.

Using a battery of behavioral measures in combination with neuropharmacological assessment should lead to a better understanding of the functional role cholinergic circuits and their receptors play in tinnitus pathology. This could lead to identification of novel drug targets. Furthermore, understanding the dynamics of these circuits could lead to improved behavioral approaches to modifying the attentional features of tinnitus.

Notes:

Status: Ongoing

DRUGS TO STIMULATE NEURITE REGENERATION FROM DAMAGED COCHEAR NEURONS

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Background

Hearing loss impairs critical communication that contributes to a decline in job performance as well as to the premature retirement of otherwise highly skilled and seasoned personnel. The financial burden of caring for affected veterans has become a major item in the VA budget. This disability is a significant problem for Military. Spiral ganglion neurons carry sound information (such as intensity, timing and frequency) from the hair cells (the primary sound receptor cells in the cochlea) to the brain. If that link is broken, either by dysfunction or death of hair cells or spiral ganglion neurons or by synapse degeneration, information cannot pass to the brain from surviving hair cells or any future regenerated hair cells.

Continuous exposure to high noise levels such as that produced by ship and jet engines and by blast exposure or weapons firing can initiate a variety of pathological changes leading to injury of spiral ganglion neurons within the cochlea, some of which occur even when the hair cells are not sufficiently damaged to undergo degeneration. The cochlear spiral ganglion neurons that originally connected to the hair cells and carried sound information can degenerate either acutely or over the long term. Hearing impairment, referred to as Noise Induced Hearing Loss (NIHL) is the result. Traumatic Brain Injury (TBI) can not only cause direct injury to hearing, but the medical interventions to treat TBI, including the administration of lifesaving, but ototoxic, antibiotics, also negatively impacts hearing. Spiral ganglion neurons degenerate by retracting their disengaged fibers from the damaged synapses and dying back toward the cell body. Degenerating hair cells and degenerating spiral ganglion neurons cannot naturally grow back, and the full complement of damaged synapses cannot naturally be restored. At present, there are no drugs that are specifically FDA approved to rescue and repair damaged spiral ganglion neurons.

One approach to the problem of damaged spiral ganglion neurons is to medically intervene to maintain survival of the neurons and stimulate the regrowth of their peripheral or central nerve fibers (neurites). Evaluating large numbers of potential drugs or unknown chemicals in deaf animal models is impractical and prohibited by complex technical factors, and excessive requirements for time and resources.

During the last funding period, we developed the first *in vitro* approach to screening small molecules for the ability to stimulate regrowth of spiral ganglion neurites. A screen of 440 compounds directly on dissociated cultures of spiral ganglion neurons, using high throughput methods for imaging 192 cultures in each experiment led us to the HMG-CoA inhibitors (also known as “statins”). Some of these statins promoted neurite elongation from spiral ganglion neurons through a part of the molecular pathway that is cholesterol independent. We elevated one statin, Fluvastatin, to more in-depth studies in noise exposed guinea pigs and our preliminary data indicated that when present during the insult, the drug protected against noise induced hearing loss.

Objectives

Screen new libraries for neurite elongating promoting activity; determine the timing (before during or after noise exposure) that is effective for fluvastatin hearing protection; Evaluate the mouse model for studies of fluvastatin protection. Objectives broadened slightly to follow up on new information. This included evaluating hair cell survival in the presence of fluvastatin, characterizing neuronal retraction bulbs (a hallmark of neural degeneration) in the cochlea under various conditions; characterizing neurites from a subclass of spiral ganglion neurons (Type II); and comparing noise responses of outbred stocks of guinea pigs provided by different breeders.

Methods

For neurite length studies, dissociated newborn mouse spiral ganglia are cultured in 384 well plates with serum and neurotrophins. Candidate compounds from public or commercial chemical libraries are added 22 hours later and the cultures are maintained for another 24 hours. Forty two chemicals can be tested in quadruplicate for each dissection. Cultures are fixed and immunostained for neuron-specific βIII tubulin. High Content Analysis is carried out by automatically imaging each well of the plate on the Xpress imager, 4 fields per well (80% of the surface area). Computer software measures neuron numbers and neurite lengths from the images. Cumulative percent histograms of neurite lengths (longest neurite per neuron) are constructed for the neurite populations in each well. For *in vivo* studies, guinea pigs are exposed to 120dB SPL noise, 4-8kHz for 4 hours. Experiment is carried out for 28 days. To deliver drugs, a cochleostomy is created surgically, and tubing attached to an osmotic pump is implanted in the cochlea to deliver the chemicals. Drugs pushed into the left ear can spread to the right ear, so hearing is assessed in the right ear which has undergone no surgery. Prevention (addition of drug 7 days before noise, Rescue (addition of drug with noise) and repair (delayed addition of drug) experiments are analyzed by auditory brain stem response (ABR) to test hearing. Hair cells are counted both in traditional histologic sections as well as by means of a novel method using hard X-rays and custom software on unsectioned cochleas. Protein expression and morphological details in the cochleas are evaluated by immunohistochemistry and confocal microscopy.

Results

<u>Fluvastatin:</u> Fluvastatin delivered 7 days before or at the time of noise exposure protects against ABR threshold shift. Fluvastatin 7 days after noise does not protect. This indicates that the drug's main actions are in the initial stages of noise induced damage. Threshold shifts are related to hair cell damage. Counts of hair cells demonstrate that Fluvastatin protects hair cells from degeneration after exposure to noise. Retraction bulbs are enlarged endings in nerve fibers that are thought to be the result of damaged cytoskeletal elements and unbalanced cellular transport. Fluvastatin reduces neuronal retraction bulbs after noise exposure. <u>Type II fibers:</u> Type II neurons are only about 5-10% of the total number of neurons and they make connections with outer hair cells. The type I, rather than the Type II, fibers are the primary sound information conduits to the brain and carry information from the inner hair cells. In most species, Type II fibers cannot be immunolabeled in adult animals and thus nothing is known about their susceptibility to noise exposure. In the guinea pig, we find that Type II fibers can be visualized with an antibody to microtubules. Noise exposure causes these fibers acute and severe damage within 24 hours of exposure, mediated at the very least by damage to the microtubules. We do not yet know the consequences of this previously unknown effect of noise on the cochlea<u>. Noise responses in two different stocks of Hartley guinea pigs</u>. Hartley guinea pigs are an outbred stock. Since there is diversity in the genetic backgrounds of animals in outbred stocks, the responses to noise among animals in the stock can be highly variable. Husbandry practices differ between breeders and could potentially be one reason that guinea pig responses to noise are so variable. We compared noise induced threshold shifts in our stocks of Hartley guinea pigs from two breeders and found that the responses to noise differed between the two stocks. Perusal of the literature indicates that source, breeding and feed of guinea pigs used in auditory experiments worldwide are not rigorously reported and may be one source of inconsistencies in guinea pig auditory experiments between laboratories.

Notes:

COCHLEAR SYNAPTOPATHY AND NEURODEGENERATION AFTER NOISE

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Background

A longstanding view of acquired sensorineural hearing loss (SNHL) has been that cochlear hair cells are among the most vulnerable elements in the cochlea and that, in the vast majority of cases, cochlear nerve fibers degenerate if, and only long after, there is loss of their peripheral hair cell targets. This view arose, fundamentally, because of the temporal offset between post-insult degeneration of hair cells and loss of the spiral ganglion cell (SGC) bodies of the primary auditory neurons with which they communicate: In animal models exposed to noise or ototoxic drugs, hair cell loss can be widespread within hours, whereas the loss of SGCs is typically not detectable for weeks to months after insult.

Recent experiments have now made it clear, at least in the noise-exposed and aging ear,[1-3] that: 1) cochlear neurons are a primary target, 2) their peripheral synaptic connections are the most vulnerable elements and 3) cochlear nerve synapses can be permanently destroyed even when hair cells survive (Fig. 1) and thresholds are normal. We also know that prior noise exposure exaggerates synaptic and neural losses that otherwise occur with age. Although cochlear synaptopathy can be hidden in a normal audiogram, it can also occur in ears with overt hearing loss and hair cell loss.

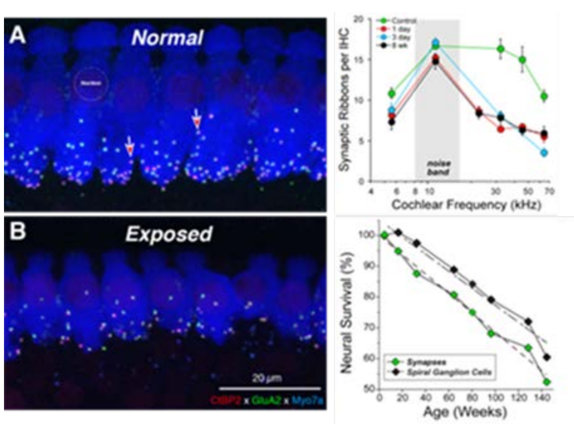

Figure 1. Immunstaining reveals pre-synaptic ribbons (red) and post-synaptic glutamate receptor patches (green) in a row of IHCs (blue). Synapses are quantified on the right, the top panel showing rapid and permanent loss after noise, and the bottom showing gradual loss (along with SGNs) with age[1,2].

This loss of cochlear synapses permanently interrupts IHC to afferent fiber communication for a subset of neurons, changing the way acoustic information is processed by the ear, even if it takes months to years for the ganglion cells to die. Neurons important for hearing out suprathreshold signals (e.g. speech) in backgrounds of noise appear to be primary targets[4]. Low-SR fiber loss also has been implicated in both tinnitus and hyperacusis (Ref. 5 for review). The basic phenomenon has now been observed in multiple mammalian species, including compelling preliminary observations in human temporal bones.

Many questions remain. We have hypothesized that a form of glutamate excitotoxicity is a primary initial event in the degenerative cascade

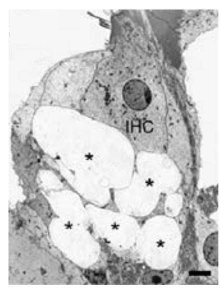

Figure 2. Excitotoxic swelling of afferent endings (asterisks) underneath the inner hair cell (IHC) can be seen after local exogenous glutamate agonist infusion or after endogenous release triggered by sound overexposure. Here, excitotoxic synaptic swelling is shown for 200 µM AMPA[6].

we have observed after noise. The afferent synapse between IHCs and peripheral terminals of SGCs is glutamatergic, and both exogenously-applied and endogenously-released glutamate (via sound overexposure) are well known to produce dramatic synaptic swelling in the immediate post-exposure time frame (Fig. 2). Although there are important similarities in the response to the two insults, there are key differences that may serve to clarify mechanisms and identify therapeutic targets. Perhaps most interesting and relevant to the current proposal, Puel and colleagues have reported that SGN peripheral terminals can recover and neurons can re-establish connections with IHCs in the days after agonist-induced insult[7], whereas losses are largely permanent after noise[1,3,4]. We will pursue this discrepancy in studies undertaken here.

Auditory nerve fibers contacting IHCs differ in spontaneous rates (SR) of firing, and their sound-driven firing rates vary over different ranges to support a large dynamic range of neural response. Threshold sensitivity is inversely correlated with SR; high-SR fibers have low thresholds but saturate at levels where high threshold, low-SR fibers continue to code level with firing rate (Fig. 3). Our studies suggest that the low-SR neurons are preferentially vulnerable to insult[4,8]. Thus, cochlear synaptopathy and low-SR neuropathy can be widespread in ears with intact hair cell populations and normal audiograms, where it has been called "hidden" hearing loss. This observation further suggests that synaptopathy should contribute to problems hearing in a noisy environment, since low-SR fibers are resistant to continuous noise masking (Fig. 3).

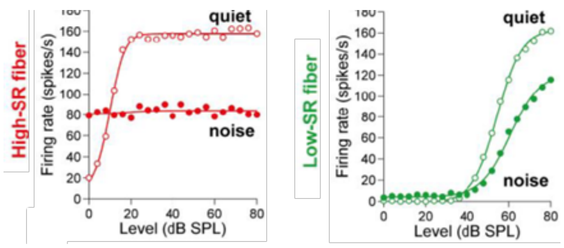

Figure 3. Rate-level functions of high- vs low-SR fibers in quiet or in presence of continuous noise. Note that the firing of the high-SR fiber saturates at low levels and is completely saturated in the presence of noise.[8]

Naval Relevance. Navy personnel are at high risk of exposure to noise, with exposures producing a variety of auditory injuries and functional impairments that compromise safety, effectiveness of communication and quality of life. Beyond the well-known threshold elevations that are a common consequence of noise exposure, loss of IHC-afferent communications should have dramatic consequences to hearing function, with or without threshold elevation. Although loss of hair cell synapses immediately silences affected cochlear neurons, the slow death of the nerve cell body and its central projections provides a long therapeutic window within which hair cells might be reconnected to the brain via therapies designed to elicit spiral ganglion neurite extension and hair cell synaptogenesis. Thus, the need for better understanding of the mechanisms and manifestations of cochlear synaptopathy is clear.

Objectives

Our long-term objectives are to better understand mechanisms and manifestations of cochlear synaptopathy and neurodegeneration in common forms of acquired sensorineural hearing loss, to develop sensitive metrics of underlying injury that can be applied non-invasively in the human to support clinical diagnosis and assay treatment effects, and to identify drugs that will target these mechanisms for prevention or repair. Here, we focus primarily on the first of these objectives by:

a) examining the involvement of pre- and post-synaptic structures and the potential for recovery after agonist- vs noise-induced excitotoxicity.

b) clarifying relative vulnerabilities of low- vs high-SR neurons to glutamate agonist and noise

c) examining the synaptic consequences of manipulations that alter synaptic strength, including their impact on the excitotoxic response to sound overexposure.

d) clarifying the functional consequences of the loss using ecologically-relevant stimuli.

Methods

In ***Aim 1***, we will employ pharmacologic and genetic tools to manipulate the contributions of glutamate excitotoxicity to post-noise changes in structure and function of hair cells, cochlear neurons and the synapses that connect them. Electrophysiologic, histologic and imaging techniques will be used to assess outcomes.

Aim 2 will employ sound exposure and genetic tools to manipulate synaptic strength. Assessment of outcomes will be undertaken as described for Aim 1. We also will characterize AMPA receptor turnover by immunostaining for, and quantifying the GluR2 subunit.

In ***Aim 3***, we will use a combination of electrophysiological and behavioral/perceptual measures, along with computational modeling of predicted outcomes to characterize the integrity of the synapses and neurons that remain/ recover after glutamate agonist- or noise-induced insults.

Results: Grant funding has not yet begun.

Notes: Background data obtained with funding from the NIH/NIDCD, Inserm, Cochlear France and the Fondation de l'Avenir.
[1]Kujawa and Liberman 2009; [2]Sergeyenko et al. 2013, [3]Fernandez et al. 2015; [4]Furman et al, [5]Kujawa and Liberman 2015; [6]Ruel et. al. 2007; [7]Puel 1995; [8]Huet et al. 2016.

Status: New

EVALUATION OF AUDITORY RECOVERY IN NORMAL HEARING ADULTS FOLLOWING TEMPORARY THRESHOLD SHIFTS

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Background

Some military personnel work in high noise environments with noise levels up to 150 dB. To minimize the risk of noise induced hearing loss (NIHL), daily noise exposure limits were developed. These limits were based on both ambient noise levels and the duration of time spent in that environment. Despite setting limits on daily noise exposure, temporary hearing losses, also known as temporary threshold shifts (TTS), have been observed after exposure to noise. TTS is considered to be early indicators that permanent hearing loss may occur in the future. Recent animal studies completed by Kujawa & Liberman (2009) have suggested that TTS cause irreversible damage to the auditory system, which can be detected with auditory evoked potentials, more specifically with auditory brainstem response (ABR). In TTS studies involving human subjects, Le Prell et. al. (2012) and Gallagher et. al. (2014) noted a complete recovery of audiometric thresholds and otoacoustic emissions (OAE) within 24 hours of the noise insult.

With complete recovery observed in a short period of time, TTS studies appear to pose no long-term risk to the human subjects involved, despite concerns raised by results from animal studies. It is worth note however, that the human TTS studies did not monitor auditory functioning over an extended period of time, nor did they investigate changes in auditory evoked potentials. Another important difference is that noise exposures and measured TTS were substantially smaller in the human studies when compared to the animal studies.

Objectives

The objective of the current study is to determine if cochlear neural damage can be detected in humans, weeks or months after a TTS is induced in a laboratory setting. Understanding the extent to which the auditory system recovers from a noise injury can lead to improvements in hearing protection, hearing monitoring programs, and noise exposure guidelines.

Methods

Up to 50 subjects between the ages of 18 and 35 years will be recruited for this study, with the goal of equal gender distribution. Qualifying subjects will complete an audiologic history questionnaire to rule out indicators of excessive noise exposure history, chronic ontological conditions, or risk factors for increased susceptibility to NIHL. Subjects will have normal hearing thresholds, normal distortion product otoacoustic emissions (DPOAE), normal middle ear function, and normal auditory-evoked potential responses, specifically ABR. Subjects will be randomly assigned into two groups: the noise group and the control group. The noise group will receive a noise dose in accordance with the schedule outlined in Table 1. Subjects will be exposed to noise using a stepped up approach to induce a TTS. Attempts to induce a TTS will occur at least 24 hours apart. After a TTS is measured the subject will not receive additional exposure. Noise doses are based on Department of Defense (DoD) exposure standards, which are more conservative than OSHA standards. The schedule is intended to induce a small TTS, defined as a deviation of ≥ 11 dB from baseline measured 2 minutes post noise exposure. At no time during the study will a subject be exposed to levels of hazardous noise greater than what is currently deemed safe by the DoD and OSHA.

Immediately following a measured TTS, post-exposure audiometric and evoked potential measurements will be completed. Results from post-exposure measurements will be compared to baseline data within subjects. The control group will not be exposed to noise. Both the control group and noise group will complete additional auditory measurements over several weeks to assess changes over time and make comparisons between the two groups.

Attempt to induce TTS	Level (dBA)	Minutes in Noise	Dose %
1	94	7.5	12.5
2	94	15	25
3	94	22.5	37.5
4	94	30	50
5	94	45	75
6	94	60	100

Notes: Minimum exposure schedule used to induce a TTS of ≥11 dB.

Results

Data collection is scheduled to begin in September 2016. The study aims to evaluate the safety of TTS studies as well as investigate the extent to which the auditory system recovers from a noise injury. Achieving a better understanding regarding issues of safety and recovery can allow for improvements in recommendations for both research methods and hearing conservation programs.

References

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Gallagher, H.L., McKinley, R.L., Theis, M.A., Bjorn, V.S., (2014). Calibration of an in-ear dosimeter for a single hearing protection device. AFRL-RH-WP-TP-2014-0002.

Notes:

Status: New

CONFIRMATORY GWAS ANALYSIS OF THE SAMPLES IN THE MARINE RECRUIT ARCHIVE

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Background
In a previous ONR-funded project, we analyzed the placebo arm of a study on the effect of N-AcetylCysteine (NAC) to mitigate noise-induced hearing loss (NIHL) in Marine Recruits. Through the discovery phase of a genome-wide association study (GWAS), we identified new biomolecular targets associated with NIHL susceptibility, including a single nucleotide polymorphism (SNP) located within the nucleolin gene and 58 other SNPs located within 17 other genes (Grondin et al, 2015).

In normal cells, nucleolin is a key regulator of apoptosis that responds to stresses similar to what cochlear hair cells experience after noise exposure. In vitro dysregulation of nucleolin increases apoptosis in cochlear hair cells undergoing oxidative stress (Grondin et al, 2015), which supports the role of nucleolin in NIHL.

This project is designed to validate the novel NIHL susceptibility markers previously identified. It will also explore the genetic of NAC efficiency in mitigating NIHL in Marine Recruits. Authors of the main Marine Recruit study highlighted the promising effect of NAC (Kopke et al, 2015), yet the potential role of genetic factor in NAC efficiency against NIHL remains unknown.

Expansion of the GWAS to achieve robust statistical significance for the genes we have identified and to assess the impact of selected SNPs in context with hearing loss will be a significant contribution to the field.

Results of this study would contribute to predict subjects at risk of hearing loss and reveal antioxidant-dependent pathways affected by NAC that will have an effect to protect subjects from NIHL.

In addition, current results of NAC efficiency on the Marine Recruits may be better understood in the light of correlations that may exist with genetic factors. It could also enable us to sort out the data from the Marine Recruit Study that shows a trend for NAC treatment. The transitional nature of this research would give much needed information on NIHL susceptibility in a population of young healthy males.

Objectives
The first objective of this project is to confirm and validate the novel NIHL susceptibility markers previously identified in the discovery phase of a GWAS, in Marine Recruits. The second objective is to genotype Marine Recruits archived samples to identify NAC efficacy in preventing NIHL.

Methods
Sample selection.
Subject samples will be selected following the criteria used during the GWAS discovery phase (Grondin et al, 2015). Briefly, subjects were in good health with normal hearing and tympanometry in both ears.
In total, 265 subjects of the placebo arm will be analyzed for the confirmation of previously identified polymorphisms and 149 samples for the NAC discovery phase.

Marine Recruits Noise Exposure
Subjects went through 10 days of small arms training and were exposed to an approximate 157 dB peak SPL impulse noise from M16 rifles. Each subject fired up to 325 rounds of ammunition and was monitored for their use of hearing protective devices, consisting of foam ear-plugs (Noise Reduction Rating of 29 dB).

Hearing loss assessment.
Audiograms, collected before and after noise exposure, are utilized to calculate the hearing threshold shift and determine the subjects with high hearing threshold shift - the cases - and subjects with low hearing threshold shifts – the controls. The threshold shift is given by the difference in average over frequencies 2, 3 and 4 kHz for each individual.

DNA processing.

DNA in saliva collected from Marine recruits and maintained in the ONR-NIHL Marine Recruit Saliva Archive are being analyzed. Samples corresponding to subjects with high and low threshold shift are being pre-processed and sent for genotyping at the Microarray Facility in the Genomics Core at Boston Children's Hospital (http://core.iddrc.org/molecular-genetics/).

Quality control and Data analysis.
Quality controls follow the standards used during the previous phase (Grondin et al, 2015). Briefly, quality controls are performed to identify outliers and sample biases by assessing heterozygozity, inbred by descent, Hardy-Weinberg equilibrium, genotyping rate, and homogeneity with HapMap population groups determined by PCA.

Results

	Sample ID range*	**Total samples**
Saliva Archive	680 - 2179	800
Audiogram data	1 - 1976	1221
Complete samples	680 - 1976	715

Table 1. Database summary of samples. (*) Sample ID is discontinued.

Saliva samples from MCRD1 study conserved in Oragene kits were provided by NMCSD. Sample IDs range from 680 to 2179 in nonconsecutive ID numbers and correspond to 800 unique identifiers (Table 1).

Corresponding audiogram data were kindly provided by Sara Murphy at NMCSD. They consist of 621 audiogram data for subject IDs ranging from 1 to 1022 and 600 audiogram data for subject IDs ranging from 1102 to 1976.
In total, 715 samples have matched audiogram data (Table 1).Quality of the saliva archive and matching audiogram data was reviewed in preparation of the study.

Hearing threshold shift between pre- and post-impulse noise exposure as the mean of hearing changes at frequencies 2, 3 and 4 kHz for subjects in the placebo and NAC arm of the study show strong overlap (fig. 1). Both distributions show a threshold shift that peaks at about 0 dB.

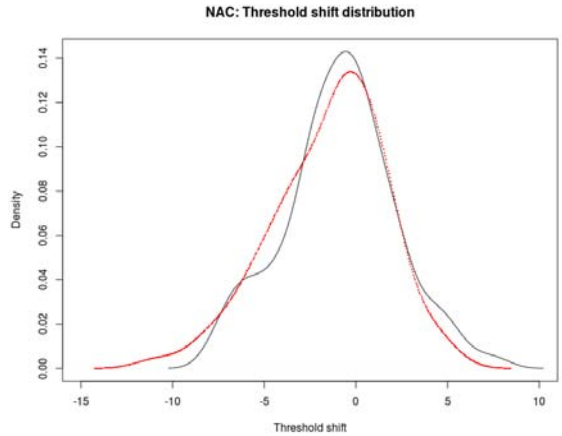

Fig.1. Density distribution of threshold shift (dB) for study subjects in placebo and NAC arms. Mean threshold shift over frequencies 2, 3 and 4 kHz is shown for placebo (red) and NAC (black), before and after noise exposure.

References.
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Notes:

Status: Ongoing

CAPTURING NEURAL BIOMARKERS OF AUDITORY ATTENTION (YIP AWARD)

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Background

The long-range vision of our laboratory is to create, within 25 years, a revolutionary assistive hearing device that will selectively amplify a signal of interest based on listener intent. We propose to achieve this by reading brainwaves non-invasively and classifying them into different human cognitive states using electro-encephalography (EEG). This work effort benefits the Navy / Marine Corps in two ways:
i. For warfighters who sustain noise-induced hearing-loss, this research can improve hearing-aid performance in a crowded environment.
ii. This research can also improve communi-cations for normal-hearing Warfighters who work in noisy operational environments with new "hearable" designs.

Objectives

Our main objective is to use a combination of psychoacoustics experimentation along with non-invasive neuroimaging techniques to track the listener's attention in the face of other distracting signals. The original experiment we proposed to carry out was to classify EEG signals as the listener is attending to two streams of discrete utterances and track the attention when a distractor (e.g., a siren) appears in the competing stream.

However, we recognize that a series of single utterances is not a natural listening scenario. Fortunately, due to the promising results reported last year, we extended our statistical model and are now confident that we can classify brainwaves as listeners attend to continuous speech as well. Therefore, we redesigned a new behavioral experiment based on attending to one of two continuous speech streams and track the attentional focus of the listeners when the speaker suddenly shifts in location. The objective is to classify listener brainwaves to identify the moment when they are exogenously attracted to the speaker at a different location.

Methods

Behavioral: In this new experimental paradigm, we ask subjects to listen to one of two simultaneous stories and periodically quizzed them about its content. We trimmed audio-book stimuli and played two stories concurrently and asked the listener to attend to one narrator and ignore the other. We present 9 blocks of stimuli and each block contains 1-8 minutes of stimuli. There is one male narrator and one female narrator and they are convolved with different head-related transfer functions to generate a spatial percept that they are 45 degrees to the left / right of midline.

Occasionally, at natural breaks in these stories, the narrators would switch sides. Since the task of the listener is to attend to the story of one narrator, one must switch spatial attention once they hear the narrators have switched sides. In order to verify whether these subjects are attending to the narrator we specified, subjects had to answer 3-4 multiple-choice comprehension questions every 1-2 minutes.

Attention classification: Previous studies suggest that sound encoding in the auditory cortex depends on attentional state of the listener. Hidden Markov models have been used to decode the attentional state of the listener by dynamically tracking the changes in the dependence between the envelope of the speech waveforms and the cortical responses recorded via MEG/EEG signals over time. Assuming a two-state linear dependence, the Temporal Response Functions (TRFs) are traditionally learned from data recorded in separate sessions by prompting subjects to attend or ignore certain speech signals. Implicit in this method is the assumption that the level of attention is sustained across sessions, which is not a behaviorally valid assumption. Moreover it is likely that subjects unintentionally switch their attention to an undesired source.

We recently extended the traditional two-state linear model to a Bayesian continuous state space model to better capture the regression time-variance by learning the "eigen-TRFs" – a basis for the auditory response kernel – and their associated time-dependent activations. These activations are then used for attention-state classification. Suppose an acoustic stimulus signal with envelope s_t is presented to a subject, evoking the auditory neural response r_t. In our model, the response is assumed to be generated by the following regression model:

$$r_t = \mathbf{s}_t^T G \boldsymbol{x}_t + v_t \ ; \ v_t \sim \mathcal{N}(0, \sigma_v), \qquad t = 1, \cdots, T$$
$$\boldsymbol{x}_{t+1} = \boldsymbol{x}_t + \boldsymbol{u}_t \ ; \ v_t \sim \mathcal{N}(0, \Sigma_u)$$

Results

In the first experiment, we used only one eigen-TRF in the above regression model to generate a simulated neural response to an input signal whose samples were drawn from a normal distribution with zero mean and unit variance. For this experiment, we chose a sampling frequency F_s of 1000 Hz and stimulus duration of 10 s (T = 10,000). To generate the response signal, we used a lagged sinc function of length 140 ms as the TRF. The activation (state) variable $\boldsymbol{x}_t$ was chosen to be a sinusoid with a total of 1 period within the whole duration. The response was then synthesized by introducing white Gaussian noise to the input envelope filtered by the time-varying TRF. Fig. 1 shows the accuracy of the method in recovering the state variable when only one-eigen-TRF is to be accounted for using this approach.

In the second experiment we generated a model consisting of two eigen-TRFs and used three different estimation models to see how the choice of the number of eigen-TRFs affects the outcome of our proposed method and how the proposed method compares with the least squares method traditionally used in the attention tracking problem (Figure 2; Table 1).

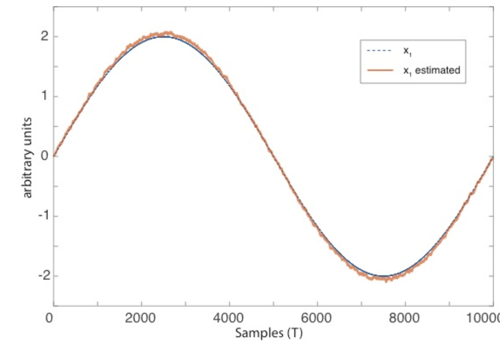

Fig.1. True and estimated state variables (activations) based on 1 eigen-TRF. Our method can accurately track the simulated attention state over time.

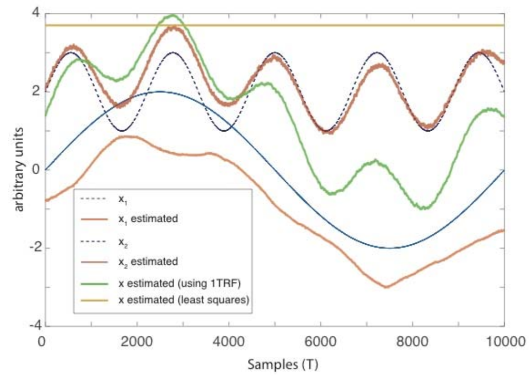

Fig.2. True and estimated state variables (activations) based on 2 eigen-TRFs. Based on the conventional approach using only 1 eigen-TRF as attention-state estimation, the error is much bigger than our approach which can track multiple TRFs.

	Prediction MSE
Least Squares	42.77
Bayesian Regress. (1 TRF)	3.25
Bayesian Regress (2 TRF's)	**2.78**

Table 1: Our method (bold) has the minimum mean-square error compared to the conventional approaches based on least squares or using only 1 TRF. Note that the substantial error associated with the least-squares method highlights its inability to track state (attentional level) across time (See Fig. 2, yellow line).

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Notes:

Biophysiokinetic effect of NIR on cochlear oxidative stress and TTS/ Integrated Test Platform for NIHL studies/ Reprogrammed Cochlear Resilience to Inflammation and Apoptosis

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Background

We sought to investigate metabolic mechanisms responsive to oxidative stress biochemical challenges found in the cochlear microcellular environment. Non-invasive biomolecular down regulation of proinflammatory intracellular metabolic pathways and suppression of oxidative stress via photobiomodulation may have the potential to develop novel therapeutic approaches to address noise exposure and ototoxic compounds associated with hearing loss. We report reduced inflammatory cytokine and mitochondrial oxidative stress levels resulting from near infrared (NIR) treatment applied to cells before gentamicin- or lipopolysaccharide- treated HEI-OC1 auditory cells.

Objectives

In this study, we investigated the effect of pre-conditioning of cells in vitro with NIR irradiation modulated oxidative stress, mitochondrial function and inflammation in HEI-OC1 cells derived from the organ of Corti from the mouse cochlea. Since this cell type is exquisitely sensitive to redox damage, we applied experimental conditions to induce oxidative stress using a bacterial toxin or an ototoxic drug. Cells were challenged with gentamicin, a widely used ototoxic aminoglycoside antibiotic that promotes the formation of Reactive Oxygen Species; and lipopolysaccharide (LPS), a bacterial-derived endotoxin that stimulates the transcription and release of proinflammatory cytokines.

Methods

Oxidative stress characterization was performed in vitro using fluorescent cell-permeable dyes. Intracellular ROS levels were measured by cell permeable dye CellROX and DCF-DA, intracellular NO levels by specific marker DAF-FM, mitochondrial superoxide by MitoSOX and the superoxide levels by dihydroethidium (HE). Evaluation of proinflammatory cytokines IL-6 and IL-1β expression was determined by multiplex magnetic bead–based immunoassay

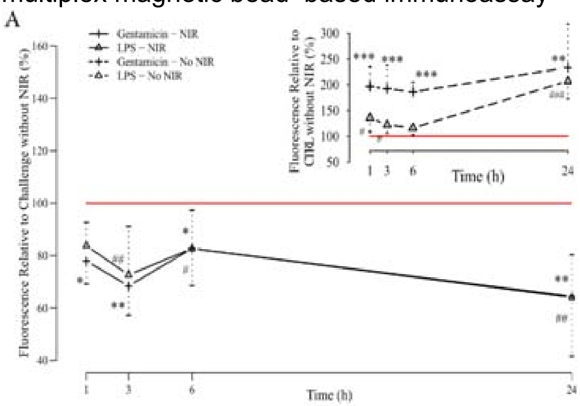

Fig.1. NIR reduces oxidative stress. NIR reduces ROS levels in cells challenged with gentamicin or LPS. ROS levels determined by flow cytometry and quantified by the fluorescent intensity of CellROX

Results

Our results show that NIR exposure mitigates oxidative stress response in HEI-OC1, a cochlea-derived cell line, challenged with gentamicin or LPS by modulating mitochondrial activity, mitochondrial superoxide, cellular ROS and NO levels. In addition, NIR exposure was correlated with a reduction in the production of proinflammatory cytokines IL-1β and IL-6. These results suggest that NIR applied to auditory cells in situ may represent an effective tool to control and limit cochlear oxidative stress and induction of localized cochlear inflammation within the organ of Corti. Thus making NIR a potential therapeutic candidate to address high levels of oxidative stress in cochlear auditory cells exposed to ototoxic drugs such as gentamicin or resulting from occupational noise exposure.

Notes:

Status: Ongoing

GLATIRAMER ACETATE (COPAXONE) TREATMENT OF NOISE-INDUCED HEARING LOSS

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Background

In a previous review, we reported the positive outcome of a study designed to evaluate the efficacy of a novel hearing loss (HL) prevention/treatment strategy involving an immunomodulatory compound with well-established neuroprotective properties (Gentile et al., 2013). The compound in question is glatiramer acetate (GA), the active agent of a drug otherwise known as Copolymer 1, Cop-1 or Copaxone, an FDA-approved drug commonly used for the treatment of relapsing-remitting multiple sclerosis. The primary finding from that investigation was that the degree of recovery from noise-induced hearing loss was significantly enhanced by treating inbred CBA/J mice with the immunomodulator prior to noise exposure. In addition, when considering inflammatory cytokine expression levels, the significant up-regulation of an anti-inflammatory cytokine and down-regulation of pro-inflammatory cytokines observed are consistent with the *a priori* view that manipulation of the immune system is an effective NIHL prevention/treatment strategy.

In the interim, the project was transferred to an outbred mouse model to more accurately assess the translational value of the treatment strategy. In the initial study, the protective properties of GA alone were evaluated by administering the compound prior to noise exposure to test its protective capacity. In this phase of the investigation, the efficacy of GA, and GA combined with N-acetylcysteine (NAC) as a treatment option for existing hearing loss were considered. The essential hypothesis was that the combined action of GA and a compound with antioxidant-promoting properties will enhance overall recovery from noise-induced hearing loss (NIHL).

Objectives

The specific objective of this investigation was to determine if the oto-protective action of GA is complemented by concurrent treatment with the antioxidant-promoting compound NAC. Treatment protocols employing antioxidant therapy that have been evaluated in recent years have produced promising outcomes (Ohinata et al., 2003; Campbell et al., 2007, 2011; Choi et al., 2008; Samson et al., 2008; Kopke et al., 2000, 2002, 2005; LePrell et al., 2007) and inspired our decision to consider the possibility that an immunology-based treatment strategy might be enhanced when combined with agents promoting free radical scavenging. Our ultimate goal continues to be the determination if GA therapy alone or in combination with other potential oto-protective agents substantially reduces the amount of permanent hearing loss and/or accelerates the rate of recovery from noise-induced threshold shifts in an outbred animal model exhibiting polymorphisms as a prelude to clinical studies.

Methods

Awake and unrestrained NMRI mice were exposed to an octave band of white noise centered on 11.3 kHz and presented at 97 dB SPL for one hour. We have shown that this exposure condition produces the hearing loss profile targeted in proposed studies; i.e., immediate post-exposure threshold elevation of approximately 60 dB followed by a brief period of recovery from temporary hearing loss leading to a permanent (residual) hearing loss in the range of 40 dB relative to pre-exposure baseline values (Walsh et al., 2016).

GA was administered in sequential doses (100 mg/kg) on a daily basis for the first 10 days following noise exposure, beginning on the day of exposure. In a separate group, GA was administered as described above, and NAC (325 mg/kg) was administered twice daily for the first 3 days following exposure, also beginning on the day of exposure. Saline (0.9%) was administered to age-matched control animals using the same dosing schedule and relative volumes as used for treated animals.

Following determination of control, baseline thresholds, hearing sensitivity was assessed immediately after noise exposure and was tracked thereafter to evaluate recovery from NIHL using auditory evoked brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs).

Results

The most relevant preliminary findings reported here are that GA alone enhanced post-exposure recovery in the outbred mouse model, and treatment with the GA/NAC combination further enhanced the degree of recovery under some stimulus frequency conditions. This was particularly notable when considering threshold recovery from NIHL at frequencies within and approximately one octave above the center frequency of the exposure band. The overall outcome pattern is evident by the 7th post-exposure day.

As for our efforts to relate treatment outcomes to inner hair cell (IHC)-auditory nerve fiber (ANF) synapse pathology resulting from traumatic noise exposure, early findings indicate that IHC-ANF synapses are reduced in number following noise exposure and subsequently restored in drug treated animals.

Discussion

Based on findings reported here, we tentatively conclude that manipulation of the immune system to promote the synthesis and release of anti-inflammatory proteins and a subset of growth factors is a promising novel NIHL treatment strategy.

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Notes:

ROLE OF FGF SIGNALING IN THE REGENERATION OF THE COCHLEA AND VESTIBULAR ORGANS

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Background

Hearing and balance disorders are very common among both military veterans and the general public, with nearly 30 million Americans affected by some form of hearing loss. The permanent nature of noise-induced hearing loss (NIHL) can be attributed to the fact that the mammalian inner ear is unable to regenerate sensory hair cells after noise trauma. In contrast, the ears of nonmammalian vertebrates are able to quickly regenerate hair cells after injury. The regenerative ability of the avian inner ear is particularly robust and has become a widely studied model of sensory regeneration.

Objectives

Our pilot studies suggested that activation of the fibroblast growth factor (FGF) signaling pathway is a critical feature of cochlear regeneration in birds. Other studies have shown that FGF signaling is essential for the proper embryonic development of the mammalian cochlea. Based on these observations, we hypothesize that reactivation of FGF signaling in the injured mammalian ear might lead to sensory regeneration.

Methods

We are using newly developed transgenic mouse models to determine the effects of reactivating FGF signaling in the mammalian cochlea and vestibular organs after acoustic trauma and ototoxic injury. Other studies have examined the role of FGF signaling in regeneration using organotypic cultures of the chick cochlea and utricle, and the lateral line organs of zebrafish.

Results

In my talk, I will review our studies focused on the role of FGF signaling in the vertebrate ear. Activation of FGFR1 results in limited regenerative proliferation in the injured cochlea. Our current data also suggest differing roles for FGF's in the development and regeneration of the auditory and vestibular organs. Finally, we have obtained evidence for a novel FGF-mediated signal between the cochlear sensory epithelium and stromal tissue that is necessary for the maintenance of auditory progenitor cells.

Notes:

Notes:

Status: Ongoing

Novel transcription factors for regeneration of functional outer hair cells after noise injury

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Background

Noise-induced hearing loss (NIHL) affects millions of navy service members even when the best protective devices are used. To address the Naval Global War on Noise (Naval Safety Center, 2007), we propose here, as a long-term goal, to develop therapeutics which would provide a framework for hearing restoration in naval servicemen who are suffering from NIHL.

NIHL is primarily caused by damage to sensory outer hair cells (OHCs) of the inner ear. Thanks to the ONR support, we have recently shown that supporting cells (SCs) can be transdifferentiated into new HCs via overexpression of the transcription factor Atoh1. Although the new HCs survived for more than 3 months in vivo, new HCs formed in this manner were immature and lacked the expression of Prestin, a terminal differentiation marker of functional OHCs. Identifying transcription factors (TFs) other than Atoh1 that promote OHC maturation is therefore important for restoration of hearing in service members suffering from NIHL.

Objectives

1. To identify combinations of novel TFs which promote OHC conversion and maturation;
2. To identify small molecules which promote OHC conversion and maturation.

Methods

- Optimize in vitro assays from Prestin-YFP and Atoh1-Cre;tdTomato mouse inner ear stem cells/otospheres for high-throughput screen;
- Perform RNA-Seq analysis of isolated OHCs, IHCs, SCs, and newly converted HCs (cHCs);
- Characterize adult mouse models with combinatory gene manipulations for HC regeneration;
- Screen for small molecule activators of Pou4f3.

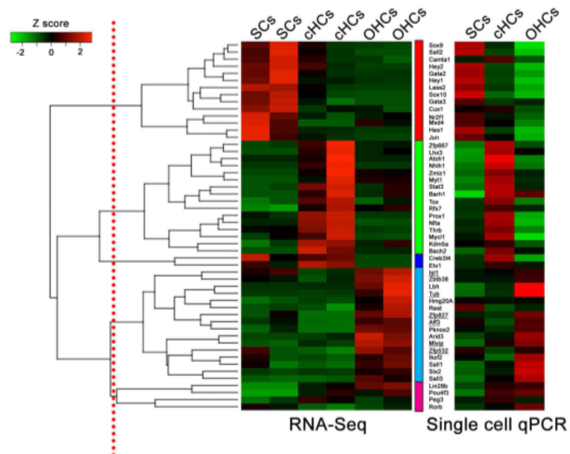

Fig. 1: Identification of 52 transcription factors that were differentially expressed between SCs, cHC, and OHCs by RNA-seq and single cell-qPCR analyses (heatmaps). Red line indicates statistical significance. 52 genes are grouped into 5 categories and Isl1 and its six targets are in cluster 4 (blue).

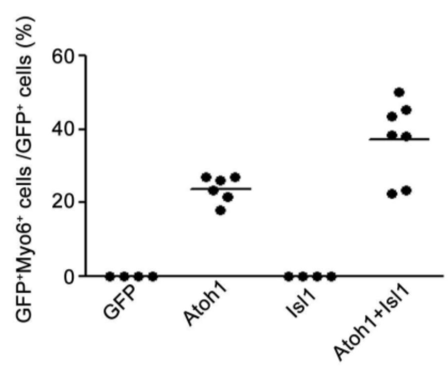

Fig. 2. Synergy between Isl1 and Atoh1 in promoting HC conversion by doubling the conversion rate (GFP+;Myo6+ cells/GFP+ cells) in cochlear explants.

Results

1. We have generated millions of cochlear stem cells in vitro that can further differentiate into mature OHCs (Walters et al., 2015);
2. We have identified 52 TFs for HC formation and maturation and validated Isl1 as a co-factor of Atoh1 in promoting HC conversion (**Figs. 1, 2**);
3. We have identified a combination of factors (Atoh1, p27, Gata3, and Pou4f3) that promote in vivo HC formation and survival in postnatal and adult mouse cochleae;

4. We have identified Pou4f3 as a TF that promotes OHC formation and survival in vivo and initiated a drug screen for small molecule activators of Pou4f3 transcription.

Notes:

Status: Ongoing

NOISE DOSIMETRY FOR TACTICAL ENVIRONMENTS

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Background

MIT Lincoln Laboratory (MIT LL) proposed to assist ONR in comprehensive collections and analysis of noise dosimetry from tactically relevant military environments. The efforts aim to improve understanding of auditory damage in the military and refine standards for noise-exposure limits to protect the Warfighter from hearing injury.

Objectives

MIT LL has supported noise-dosimetry efforts for military exercises and analyzed recent and legacy data sets to help characterize the link between noise exposure and auditory damage. We aim to provide dosimetry support in conjunction with other physiological measurements, such as audiometric or genetic, to support development of damage risk models, metrics, and therapeutics for NIHI.

Methods

In an effort to improve understanding of auditory damage metrics in tactical environments, we analyzed hundreds of hours of noise measurements collected during a 2014 Joint Strike Fighter (JSF) exercise on an aircraft carrier. The collection, organized by Noise Control Engineering, LLC., included 24h persistent noise measurements from berthing rooms of the aircraft carrier CVN-68 during a JSF exercise. We characterized recovery conditions for service members for periods where flight operations were active versus inactive and evaluated damage risk metrics on the complex noise environment.

Additionally, leveraging legacy data sets such as the chinchilla blast overpressure studies from United States Army Aeromedical Research Laboratory (USAARL) and the Auditory Research Lab at State University of New York (SUNY) (Hamernik et al., 1998), which include exposure and audiometric data, we evaluated and compared proposed auditory damage metrics and have identified strengths and limitations of each metric.

Results

Fig. 1 shows average noise levels for recovery in three berthing rooms in the gallery deck (immediately below the flight deck) for an 8h period during flight operations (08:00-16:00) versus an 8h non-flight operations period (12:00-08:00). In both conditions, the Navy limit of 85 dBA for 8h is satisfied in the berthing rooms. However, implicit in the Navy limit is a presumption that personnel exposed to loud noises have a recovery period following the exposure that is at least as long as the exposure duration (Kryter, 1985). This quiet period allows the ear to recover from temporary threshold shifts and return to normal hearing levels. Ward estimated that the upper limit of “effective quiet” noise levels to support hearing recovery for resting personnel is between 65 and 75 dBA (Ward et al., 1976).

Personnel may receive a full noise dose performing duties above deck, then experience continued exposure during resting hours in the berthing rooms below deck. During flight operations, personnel at rest in the gallery deck berthing rooms are exposed to noise that exceeds the “effective quiet” levels and as a result, may not have adequate conditions for their hearing levels to recover.

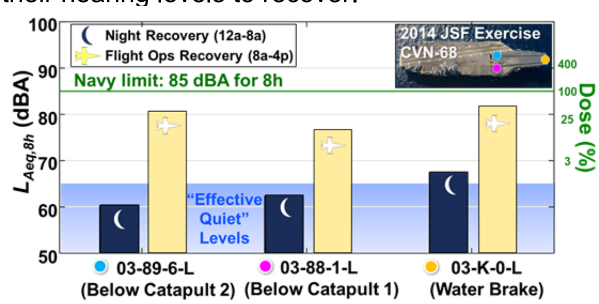

Fig. 1: Recovery conditions in berthing rooms.

When flight operations are inactive, the rooms below the catapults are sufficiently quiet for hearing recovery. However, the forward-most room, 03-K-0-L, continues to experience elevated noise levels even after flight operations conclude.

The 8-hour equivalent A-weighted noise levels ($L_{Aeq,8h}$) from Fig. 1 are examples of a damage risk metric. $L_{Aeq,8h}$ is primarily applied to steady-state background noise, but impulsive events such as weapons fire or the catapult impact from aircraft launches also pose significant risk for hearing damage. Damage risk metrics for impulse noise are an active area of research. Several metrics have been proposed including those listed in Table 1. Peak SPL and $L_{Aeq,8h}$ are current Navy damage risk metrics. Additionally, we considered a kurtosis-corrected version of $L_{Aeq,8h}$ that aims to compensate for increased risk in complex noise (Goley et al., 2011; Qiu et al., 2013) and two impulse metrics specified by the latest DoD design criteria standard for noise limits: (1) the $L_{IAeq,8h}$ metric which includes a correction factor for long duration impulses (McKinley, 2015); and (2) Auditory Risk Units (ARUs) computed from the Auditory Hazard Assessment Algorithm for Humans (AHAAH) model (Price and Kalb, 2015).

Table 1 summarizes the metrics calculated for a 24h interval from three berthing rooms. Two rooms, 03-88-1-L and 03-89-6-L, did not contain high-level impulses, so the impulse metrics $L_{IAeq,8h}$ and AHAAH ARU are not appropriate metrics for these rooms. The conventional $L_{Aeq,8h}$ and kurtosis-corrected $L'_{Aeq,8h}$ characterize the accumulation of continuous and intermittent noise energy over 24h. Applying a kurtosis correction to account for complex noise increases the equivalent levels by 1-2 dB in these rooms, but it still falls below the 85 dBA criterion. In Room 03-K-0-L, the impulse peak levels from catapult launches are much higher, exceeding 140 dB for several launches. In this room we calculate the impulse metrics $L_{IAeq,8h}$ and AHAAH ARU for high-level peaks as well as the conventional $L_{Aeq,8h}$ integrated over the full 24-hour period. The damage risk metrics give conflicting results: the conventional and kurtosis-corrected $L_{Aeq,8h}$ are close to, but below the 85 dBA limit and $L_{IAeq,8h}$ which integrates only the impulse noise (neglecting background noise) yields a very low hazard. Conversely, the AHAAH ARU metric predicts significant hazard from the impulses in this room for both Warned and Unwarned states. The inconsistencies seen between $L_{Aeq,8h}$, $L_{IAeq,8h}$ and AHAAH ARU damage risk metrics for this room emphasize the need for further research to understand the limitations of damage metrics and develop clearer guidelines on which metric or metrics should be applied in a given scenario.

Table 1: Comparison of damage risk metrics.

Metric	*Criterion*	**03-88-1-L**	**03-89-6-L**	**03-K-0-L**
Impulse Count	*n/a*	0	0	24
Peak SPL (dB)	≤ 140	123	122	143
$L_{Aeq,8h}$ (dBA)	≤ 85	75	79	81
$L'_{Aeq,8h}$ with kurtosis (dBA)	≤ 85	76	81	84
$L_{IAeq,8h}$ (dBA)	≤ 85	*n/a*	*n/a*	58
AHAAH Unwarned (ARU)	≤ 500	*n/a*	*n/a*	1800
AHAAH Warned (ARU)	≤ 500	*n/a*	*n/a*	695

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Acknowledgements

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Notes:

Status: New

IMPULSIVE NOISE AND KURTOSIS AS A METRIC TO CHARACTERIZE NOISE EXPOSURES

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Background

The 1998 NIOSH Criteria document for Occupational Noise Exposure addressed hearing damage risk criteria for continuous sounds below 140 dB SPL due to the absence of suitable epidemiologic data. Until quite recently, we had a limited ability to (1) reproduce calibrated impulsive sounds under controlled conditions and (2) accurately measure impulses in real-world occupational environments. The data for the current damage risk criterion for noise was derived from octave band data of industrial noise exposures and audiometry for individual workers who typically did not wear hearing protection. As a result the detailed analysis of the characteristics of the noise data could not be included in the development of damage criteria.

Present day digital instrumentation makes thorough recording and analysis of shift-long individual subject exposures a relatively straightforward process. NIOSH and SUNY Plattsburg have a unique opportunity to examine the noise exposure and hearing of noise-exposed workers in the heavily industrialized Zhejiang province in China who, until recently, worked without hearing protection. The data will help us develop recommended exposure limit guidelines for impulsive noise and combined exposure to noise and chemicals.

One of NIOSH's goals for hearing loss prevention is to develop damage risk criteria for impulsive noise – both complex noise and high level (>140 dB) impulse noise. In order to accomplish that goal, epidemiologic and noise recordings that are representative of worker exposures need to be collected and analyzed. Military noise exposures also include both self-generated impulse noise (e.g. weapon fire) and occupational exposures at lower levels which include impulsive and continuous noises. Impulsive noise or complex noise exposures are not adequately covered by damage risk criteria required by OSHA and DoD regulations or by NIOSH recommendations.

Objectives

1. Create a database of whole-shift (8-hour) noise assessments and hearing thresholds for a population of noise-exposed human subjects.
2. Evaluate the accuracy of the kurtosis adjusted equivalent energy metric to predict hearing loss as a function of cumulative exposure.

NIOSH will work with at State University of New York at Plattsburgh to collect data from noise exposed workers in heavy industry in the Zhejiang Province of the People's Republic of China. Full shift noise exposure dosimetry and audiometry will be collected for approximately 90 persons a month over the course of the two-year study. SUNY will conduct the analysis of the noises and hearing to evaluate the dose response relationship between complex noise exposure and hearing loss.

Data collection will be conducted through a contract with researchers SUNY Plattsburgh in collaboration with the Zhejiang Center for Disease Control and Prevention (CDC) in China. One of the main obstacles towards developing new occupational guidelines for impulsive noise is the lack of human exposure data. SUNY and Zhejiang CDC researchers have previously collaborated to examine noise exposures in the heavily industrialized province of Zhejiang where the use of hearing protection has been non-existent and only recently introduced.

Methods

Approximately 1,200 noise-exposed workers be identified and following data will be collected from the workers: noise exposure data (Time-weighted average (TWA), Dose, 8-hour equivalent A-weighted levels (LAeq8), and kurtosis) and hearing thresholds. The study will also examine up to 400 non-noise exposed industrial workers. The data will be analyzed to establish the dose-response of workers exposed to complex noise and develop and validate applicable metrics to characterize exposures to Gaussian and non-Gaussian noises (such as impact/impulse noise). Dose-response relationship will service as the basis for establishing occupational guidelines and updating the NIOSH Noise Exposure Criteria Document.

The proposed study will collect full-shift noise exposure and audiometric data on workers in diverse and complex industrial noise environments, mainly in heavy industries. The study is based upon a unique collaboration between SUNY Plattsburg and the Zhejiang Province Center for Disease Control, which has recently reviewed personnel work histories on over 18,000 employees from 25 industries under their jurisdiction. They have identified more than 7,000 workers exposed to only one industrial high-level noise environment (LAeq8 > 80 dB (A), with exposure duration varying from 2 to 40 years. Each noise exposed subject will have their personal shift-long (~8 hours) noise exposure digitally recorded, allowing for more complete noise exposure characterization. This approach is unique because it allows for the analysis of full-shift (~8 hour) recordings for a large and diverse noise exposed population. Equally important, exposed subjects will be selected based upon employment limited to a single noise-exposed industrial environment which has been stable over their working period. Subjects will have not used hearing protection during most of their working history. (Note: Hearing protection has only been introduced into selected occupational environments in China during the last 3-4 years and with little training or enforcement.) This data set will allow the construction of novel matrices to facilitate a more accurate evaluation of the dose- response relation between complex noise and NIHL, and to more fully account for age-related hearing loss independent of noise exposure. The data set is designed to be large enough to go beyond simple statistical significance and provide practical and precise estimates of the parameters necessary to predict NIHL.

Task 1: Study Design. Study setup and organizational arrangements will be discussed and agreed upon by all parties. Zhejiang CDC will start initial screenings of subjects and identify study sites. SUNY and Zhejiang CDC will be responsible for ensuring that data collection on individuals follow IRB protocol required in the data collection site and meet all applicable laws and regulations. SUNY and Zhejiang CDC will also be responsible for the training and instructions of technicians, industrial hygienists, and audiologists on proper collection of noise measurements, subject tracking, collecting surveys and questionnaires, and administering of routine otologic and biometric exams.

Task 2: **Data Collection Equipment**. Noise measurement and hearing screening equipment will be identified and acquired as proposed (30 sets of noise dosimeters and recorders, 4 sound level meters, 4 audiometers, 4 acoustic calibrators, and supportive peripherals and software). IT equipment and supporting supplies will also be identified and purchased as proposed. NIOSH will provide recommendations on the proper selection of equipment. All equipment must meet appropriate ANSI or IEC standards. Zhejiang CDC senior consultants will be responsible for the proper training, preparation of equipment for noise measurements, and identifying subjects and noise sources to be measured.

Task 3: **Initiate data collection**. Noise exposure and hearing screening will be collected at a rate of about 90 subjects per month. At the end of each month, data collected in the field will be shared with NIOSH for archiving purposes and subsequent analysis. A standard for exchanging data that ensures privacy, safe handling, and proper storage of the data will be agreed upon. No personal identifiers will be provided in the data that will permit linkage back to the worker in China.

Results

As of 5 AUG 2016, the interagency agreement has not be finalized. The contract with SUNY Plattsburg is ready to be awarded so that data collection may commence.

References

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Disclaimer

The views and the opinions expressed within this paper are those of the authors and do not represent any official policy of the Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health.

Status: Ongoing

COMBAT INFORMATION CENTER PERFORMANCE IN NOISE EXPERIMENT

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Background
Garinther and Peters (1990) demonstrated the impact of impaired communications for a U.S. Army tank crew in a simulated battle. The crews were less effective attacking adversaries and more likely to be destroyed when their audio communications were disrupted. The noise level to which a crew member of a Naval vessel will be exposed depends on locations the crew member occupies during their day and the level of noise which ship operations are producing in those areas. In spite of a challenging audio environment, verbal communication remains a vital path for the flow of information and commands aboard ship and between ships.

Objectives
The goal of the Performance in Noise (PiN) project is to extend the Garinther and Peters finding to a Naval Combat Information Center (CIC). The basic experimental design, established in the first experiment (Mentel et al, 2013), includes tasks typical for an ARLEIGH BURKE Class Aegis guided missile destroyer (DDG), which require decisions by and communication between participants and experimental confederates. The experiments have been completed so far. The first two experiments demonstrated the compromised hearing did alter operational performance, but also that Sailors employed a number of compensation strategies to sustain performance in the face of compromised hearing. Each experiment sought to extend previous findings and feedback from our participants. As a result, the overall workload was increased by adding more events designed to increase team interaction, increased realism by adding a Chat function, increased friendly resources including a Scan Eagle UAV and a collation ship, as well as increasing the number and variety of unknown and hostile vessels and aircraft. Finally, countable responses have been integrated into the natural flow of the scenario.

Methods
First and foremost, experiments such as these require experienced participants who are qualified to stand watch on a CIC, and equally qualified confederates. Then, a well thought out and rehearsed mission scenario, and finally, computer hardware and software to create a simulated CIC environment, the means to control the hearing abilities of the participants and collect experimental data.

The experimental CIC was organized into four watchstations that interacted through voice communications and computer displays to fulfill the ship's mission. Communications were primarily achieved through two communication networks, identified as Net 15 and a radio telephone (RT) circuit. Participants monitored both concurrently. Net 15, heard in the right ear, was used to handle intra-ship communications between key ship control, weapons, engineering, and combat systems support functions. The RT circuit, heard in the left ear, was used for communications external to the ship. Each watch station had three computer displays. The primary visual display was the Tactical Situation Display (TACSIT). The TACSIT was a dynamic digital map displaying objects in the environment in relation to the Sailors' own ship. Surface and Air targets were displayed using standard symbology, which also indicated track designation as either unknown, friendly or hostile. When selected or "hooked", additional information about the track such as speed, altitude and heading was displayed. A second computer monitor showed images from the ship's Optical Sight System (OSS). And the final monitor displayed a text-only chat window, which provided real-time text messages.

With the simulated CIC in place the confederates followed an outline of events making calls from various on and off-ship sources, tracks appeared and progressed on the TACSIT, and chat messages appeared according to a pre-determined schedule. This provided the simulated tactical environment for the participants to complete their mission.

The scenario was divided into eight segments and an initial dry run to familiarize the participants. One of four hearing conditions was assigned to each segment. The signal to noise ratio (SNR) (white noise to voice) used in each condition was established during an adaptive modified rhyme test (aMRT) given to all participants at the beginning of the experiment. The aMRT adjusted the SNR after each trial to determine the unique SNRs which produced SI levels of 40, 60 or 80 percent. Thus, regardless of difference in hearing, all participants were working with the same SI levels in addition to no noise or an SI of 100%.

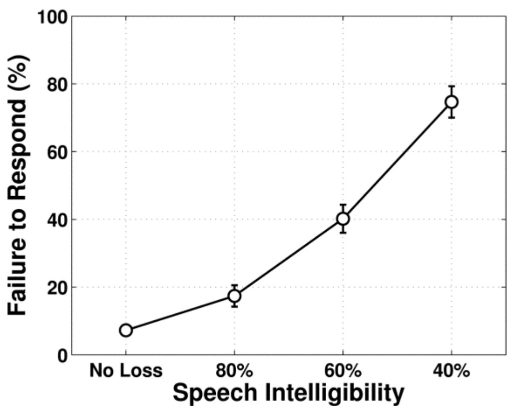

Fig.1. Percent of direct communications with no response by SI level. Mean percent failure to respond with error bars representing plus or minus one stand deviation.

Results

Overall, the manipulation of hearing ability as individually determined SI levels rather than as a range of SNRs, as was done in the first experiment, produced more consistent data. Figure 1, for example, shows the percentage of messages directed to a participant which the participant failed to respond to in any way. Clearly, as SI declines, the likelihood that a message will not generate even an acknowledgement increases substantially.

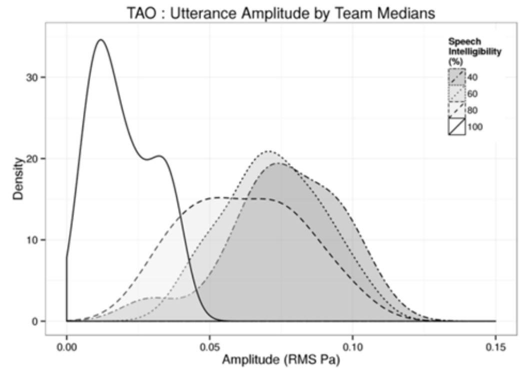

Fig.2. A density plot of the median utterance amplitude at each SI level. The utterance amplitude increased substantially at any SI level below 100%.

Changes in hearing are not the only effects. The speaker also changed their behavior, as show in Figure 2. Other measures show changes in behaviors not directly related to hearing, such as visual attention based on eye tracker recordings.

These non-auditory changes suggest that the impact of impaired hearing extends beyond the obvious initial effects on hearing and speech and into other portions of watchstander duties and even to other watchstanders. Characterizing these indirect effects on operational performance will make clear the benefits of noise abatement and hearing protection to Naval operations.

Notes:

BEHAVIORAL MEASURES OF THE PRECISION OF CODING OF INTERAURAL TEMPORAL DISPARITIES IN HUMAN LISTENERS

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Background

The binaural system plays a fundamental and predominant role in our ability to localize sounds, to understand conversation in noisy and/or reverberant environments. The predominant cues for binaural processing are interaural temporal differences (ITDs) both in terms of human binaural function and in terms of what has been learned about binaural processing via their study.

Explanations of ITD-based processing rely on sets of "internal delays" that compensate for and/or allow one to estimate the ITDs of sounds arriving at the ears. Despite its fundamental role, surprisingly little is known regarding how the precision of the "internal" coding of ITDs varies with their magnitude (related to a sound's azimuthal position) and the frequency region of the sound. While such fundamental aspects of ITD-processing are poorly understood for young, normal-hearing listeners, even less is understood regarding how degradations of ITD coding may be age-related and/or may be associated with or result from even "slight" hearing loss. Behavioral manifestations of such losses in human listeners have, to date, been rather elusive. Our recent findings strongly suggest that we have discovered a central, binaural ITD-related neural manifestation of such deficits.

Objectives

A major objective is to provide empirical data and quantitative analyses that characterize the precision of ITD-coding as a function of ITD-magnitude and center frequency. One primary goal is to evaluate how audiometrically-defined "slight" or "hidden" hearing losses might be associated with deficits and/or changes in binaural processing via degradations in precision of ITD-coding. A second objective is to evaluate how changes in precision of ITD-coding affect the perceived lateral positions of sounds. A third objective is to use the empirical measures to make informed adjustments to a cross-correlation-based model of binaural processing in order to evaluate the degree to which the model can account for changes in the perceived laterality of sounds on the basis of changes in the central ITD-precision function that, in turn, may stem from slight hearing-losses, hidden hearing-losses, and/or age.

Methods

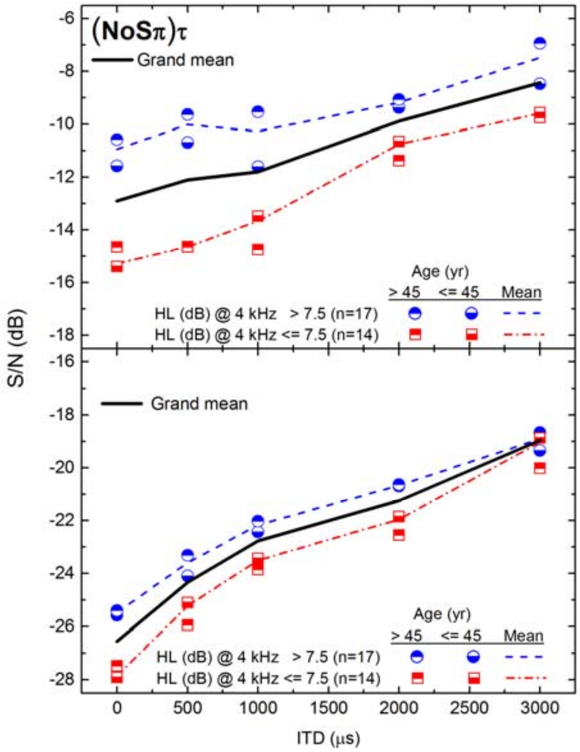
Data are obtained from human listeners ranging in age from about 20 to 70 years, all having pure-tone thresholds (250 Hz to 8 kHz) not exceeding 25 dB HL. Thus, all listeners are classified audiometrically as having normal thresholds or as exhibiting "slight loss."

Binaural detection and discrimination thresholds are obtained via a novel set of stimulus configurations that yield measures that allow one to quantify precision of ITD-coding. Data are also obtained in an acoustic "pointing" task that yield measures of perceived extent of the laterality of sounds.

Results

Figure 1 contains data obtained from 31 listeners who fit the criteria described above. Data were obtained at 500 Hz and at 4 kHz employing the $NoS\pi$ configuration (masker interaurally identical, signal phase-reversed) subsequent to imposition of an ITD on the entire signal-plus-masker waveform. We call that configuration $(NoS\pi)\tau$. Within each panel of the figure, the S/N (dB) yielding 71% correct is plotted as a function of ITD. The heavy solid line represents the grand mean across all 31 listeners. Note that thresholds increase monotonically with ITD. *This suggests, and analyses indicate, that precision of ITD-coding decreases with ITD.* The dotted and dash-dotted lines represent the respective means for listeners having thresholds at 4 kHz that were <= 7.5 dB HL or > 7.5 dB HL. The data reveal that the listeners having values of HL > 7.5 dB HL required, *for all values of ITD tested, larger signal-to-noise ratios in order to detect the signal.*

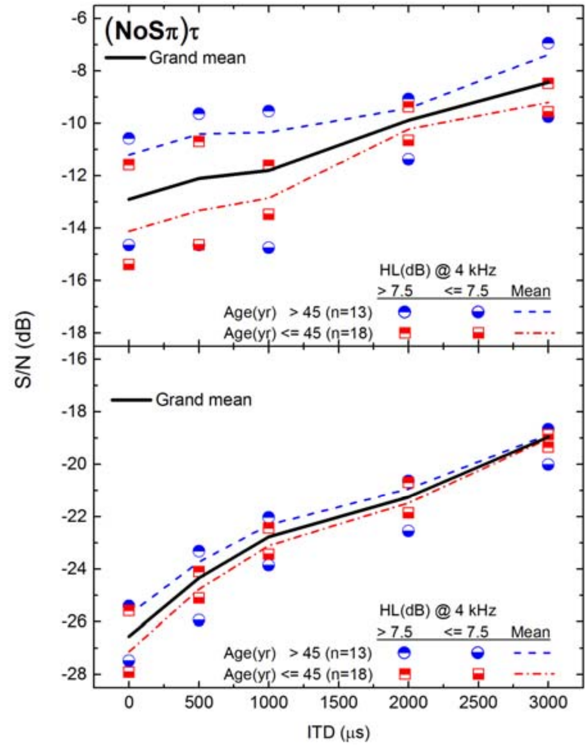
The data in Fig. 1 were also partitioned by age (>45 yr or <=45 yr) and are represented by the half-filled symbols. Symbols with top halves filled represent mean thresholds from listeners aged >45 yr; symbols with bottom halves filled represent mean thresholds from listeners aged <= 45 yr. For the data obtained at 4 kHz and at 500 Hz, in almost all cases: 1) detection thresholds for listeners having hearing thresholds >7.5 dB HL fall above the grand



mean regardless of age; 2) binaural detection thresholds for listeners having hearing thresholds <= 7.5 dB HL fall below the grand mean regardless of age.

Fig.1. Binaural detection thresholds. Data partitioned first by HL and then by age.

Fig. 2 follows the same format as Fig. 1 except the data were first partitioned by age and then further partitioned by hearing threshold (<=7.5 or >7.5 dB HL). Symbols with their top halves filled represent mean thresholds from listeners having HLs @ 4 kHz > 7.5 dB; symbols with their bottom halves filled represent mean thresholds obtained from listeners having HLs @ 4 kHz <= 7.5 dB. Note that the half-filled circles and half-filled squares are neither consistently separated from each other nor clustered near their respective means, as was the case for the



repartitioned data in Fig. 1. The data strongly suggest that age, per se, is not determinative of sensitivity to ITD.

Fig. 2. Binaural detection thresholds. Same as Fig. 1 except that the data were partitioned first by age and then by HL.

The comparisons described above support the proposition that differences in the precision of ITD-coding are more likely attributable to differences in hearing threshold than to differences in age. Most importantly, the data strongly support the hypothesis that *even listeners whose high-frequency monaural hearing status would be classified audiometrically as being normal or "slight loss" may exhibit substantial and perceptually meaningful losses of binaural processing.*

Notes:

Status: Ongoing

USMC ACOUSTIC INJURY INCIDENCE, PROGRESSION, AND GENETIC RISK FACTOR ASSESSMENT

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Background

Tinnitus and hearing loss are the most prevalent service-connected disabilities of new compensation recipients (FY15 Annual VA Benefits Report). In 2006, an Institute of Medicine report estimated the prevalence of noise-induced hearing loss (NIHL) and tinnitus among U.S. Military members from World War II through 2005, and concluded that military hearing conservation programs (HCPs) had not adequately protected the hearing of U.S. service members (Humes, et al). Among occupational groups with the highest noise induced hearing injury rates, those of the “Infantry, gun crew and seaman” group was 50-100% greater than that of most of the officer and other enlisted groups. The higher rates are likely due to more frequent impulse noise exposures. Several studies have demonstrated permanent threshold shifts (PTSs) in 10% or more of military personnel during weapons training (Marshall et al., 2009; Attias et al., 1994), and two other recent studies have shown as many as 37% of Marine recruits exhibited a measurable degradation in ultra-high frequency hearing thresholds (Kopke et al., 2015), despite the enforced use of hearing protection devices (HPDs). These numbers indicate that while HPDs may effectively protect against continuous noise, they may lack sufficient protection against impulse noise in some populations.

Hearing response to noise exposure varies considerably across individuals, as observed in Marine Corps recruit studies. While recruits were a very homogeneous population and experienced similar noise exposures, hearing threshold responses varied significantly. Some recruits exhibited no hearing loss, while others exhibited significant temporary or permanent threshold shifts. Genetic predisposition may explain some of this variability. NIHL, studied in human and animal models, has been shown to correlate with numerous genes that may contribute to noise sensitivity. Single Nucleotide Polymorphisms (SNPs) in these genes may increase an individual’s sensitivity, leading to predisposition for hearing loss when exposed to excessive noise.

Objectives

1. To determine the incidence and progression of acoustic injury among Marine Corps Range Safety Instructors (RSIs). This will involve two different approaches: the first is determination of temporary threshold shift (TTS) with pure-tone audiometry (PTA), otoacoustic emissions (OAEs), Békésy-tracking and speech recognition tasks by comparing screening/baseline and post-firing test results. The second is determination of changes in hearing thresholds by comparison of audiometric testing results for post-training and post-recovery at 1, 3 and 6 month intervals.
2. To determine if pre-existing hearing loss, various behaviors, previous exposures, and/or general stress level is predictive of increased risk of TTS and/or permanent threshold shift (PTS).
3. To characterize the noise exposure conditions of Marine Corps RSIs during weapons training sessions to: a) develop individual exposure estimates for use in statistical modeling, and b) establish a standardized environment for labs to test hearing devices and countermeasures.
4. To determine if the presence of specific SNPs is associated with short-term and/or long-term NIHL in a cohort of Marine Corps RSIs administering weapons training, chronically exposed to impulse noise for up to six months.

Methods

This is a prospective cohort study to investigate the effects of impulse noise exposures on hearing in up to 100 healthy Marine RSIs assigned to oversee weapons training at Marine Corps Air Station Miramar (MCAS) and Camp Pendleton (CPEN) Weapons and Field Training Battalion (WFTBn). Following consent, subjects will complete “Demographic” and “Clinical and Noise Exposure” questionnaires. Tympanometry, a functional hearing assessment test battery [PTA, OAEs, Békésy-tracking audiometry and speech recognition tasks], completion of a “Hearing and Noise Sensitivity” questionnaire, and provision of a morning and afternoon salivary stress sample will be conducted at Baseline and at each scheduled follow-up visit (see Figure 1). Consenting subjects will also provide saliva samples for

DATA	BASELINE DAY -21 to 0	EXPOSURE WEEK 1 First Exp Day	EXPOSURE WEEK 1 Last Exposure Day	SA	SU	EXPOSURE WEEK 4 First Exp Day	EXPOSURE WEEK 4 Last Exposure Day	SA	SU
DCFs	C, D, CNEH, HNS	HNS	HNS	Recovery (infrequent exceptions in summer months)		HNS	HNS	Recovery (infrequent exceptions in summer months)	
Audiometry	MEF, PTA, Bksy, Spch, OAE	MEF, PTA, Bksy, Spch, OAE	MEF, PTA, Bksy, Spch, OAE			MEF, PTA, Bksy, Spch, OAE	MEF, PTA, Bksy, Spch, OAE		
Bio samples	SD, SH	SD, SH	SH			SH	SH		
Primary activities	Classroom instruction	Weapons training and testing				Weapons training and testing			
Noise	None	Frequent impulse noise				Frequent impulse noise			

DATA	EXPOSURE WEEK 14 First Exp Day	EXPOSURE WEEK 14 Last Exposure Day	SA	SU	LAST EXPOSURE WEEK First Exp Day	LAST EXPOSURE WEEK Last Exposure Day	SA	SU
DCFs	HNS	HNS	Recovery (infrequent exceptions in summer months)		HNS	HNS	Recovery (infrequent exceptions in summer months)	
Audiometry	MEF, PTA, Bksy, Spch, OAE	MEF, PTA, Bksy, Spch, OAE			MEF, PTA, Bksy, Spch, OAE	MEF, PTA, Bksy, Spch, OAE		
Bio samples	SH	SH			SH	SH		
Primary activities	Weapons training and testing				Weapons training and testing			
Noise	Frequent impulse noise				Frequent impulse noise			

Figure 1. Legend: C = Consent, D = Demographic Qx, CNEHA = Clinical and Noise Exposure History Qx, HNS = Hearing and Noise Sensitivity Qx, MEF = Middle Ear Function Test(s), PTA = Pure Tone Audiometry, Bksy = Békésy tracking audiometry, Spch = Speech Audiometry, OAE = Otoacoustic Emissions testing, Audiometric Tests, Q = Questionnaires, SD = Saliva DNA, SH = Saliva Stress Hormones

DNA. RSIs will be recruited prior to their first assignment-related exposure and followed for the first six months of RSI assignment. Audiometric testing will be conducted during four weeks distributed across the six month observation period. Threshold shifts will be determined using DoD significant change criteria and ASHA early detection criteria (1994). DNA from saliva samples will be analyzed using gene chip arrays to evaluate the expression of genes, and cluster analysis to determine gene linkage or association patterns between specific genes, their polymorphisms and phenotypic expressions, such as susceptibility to NIHL. Samples from this study will be combined with those from other studies to facilitate a planned, larger prospective investigation of military volunteers with similar exposures to those in this study. The aggregate cohort will provide the power needed to evaluate SNPs related to long-term impulse noise exposure.

Results

Data collection is complete for the MCAS Miramar subcohort. Subject recruitment at CPEN began with the CMC 3-16 entering Coach Class on 3/4/16. To date, 32 subjects from five entering classes have been recruited and are at various stages of protocol completion. The most recent subcohort, CMC 7-16, completed Baseline testing 8/10/16. Subject recruiting, biological sampling, and audiometric testing are ongoing. The first CPEN subcohort will complete testing the week of 9/16/16. An overview of the CPEN subcohort testing status is shown below in Figure 2.

		Testing Completed								
			Week 1		Week 4		Month 3		Month 6	
Subcohort	Subjects	Baseline	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
3-16 Field	4	x	x	x	x	x				
3-16 Charlie	4	x	x	x	x	x				
3-16 Delta	1	x	x	x	x	x				
4-16 Supply	2	x	x	x	x	x				
4-16 Delta	1	x	x	x	x	x				
5-16 Bravo	5	x	x	x	x	x				
5-16 Delta	1	x	x	x	x	x				
6-16 Field	2	x	x	x						
6-16 Charlie	3	x	x	x						
6-16 Delta	4	x	x	x						
7-16	4	x								

Figure 2. Data collection status for the CPEN subcohorts. An “x” indicates data collection completed.

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Notes:

EARLY DETECTION OF COCHLEAR DAMAGE FROM NOISE AND OTOTOXINS

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Background
This project's goal is determining the optimal methods for detecting early noise- and ototoxin-induced cochlear damage. In our previous ONR-supported work we have shown that distortion product otoacoustic emission level phase mapping (DPOAE L/P mapping) provides comprehensive information on cochlear function. We have developed a portable and comprehensive hearing assessment system (the Creare Hearing Assessment system or CHA) for measuring DPOAE L/P maps, and other tests. The system's battery of audiological tests includes DPOAE measures, the Hearing-In-Noise-Test (HINT), threshold audiometry (both modified Hughson-Westlake and modified Békésy audiometry), fixed-level frequency threshold (FLFT) testing, spontaneous otoacoustic emissions (SOAEs), gap detection testing, hearing questionnaire administration, as well as quality factor measures (in ear noise and probe position). Our data show that DPOAE L/P mapping has promise for detecting small changes in cochlear function. More work is needed on map analysis and interpretation. To develop these analysis tools, we have been collecting data on test repeatability and on cochlear/hearing damage from ototoxins and noise.

Objectives
Specific Aim I: Characterize cochlear function changes due to known ototoxins (e.g. cis-platinum). Assess DPOAE map repeatability.
Hypotheses: DPOAE L/P mapping will show changes earlier and more reliably than standard audiometry and DP grams. Maps will be repeatable over time. This aim also includes studying the repeatability of high-frequency Békésy-style audiometry, the FLFT, and SOAEs.

Specific Aim II: Use advanced statistical techniques to reveal cochlear changes on the maps. Analyze DPOAE phase characteristics to separate the DPOAE components and determine how phase and amplitude combined can improve the reliability of DPOAE measures for detecting cochlear damage. Also, test statistical methods for determining map changes over time (e.g. principal component analysis, statistical parametric mapping). Since the initial proposal we have added random field theory as a promising approach to this analysis.
Hypothesis: DPOAE are complex signals produced by the inner ear. When generated, multiple sources are combined and detected by the DPOAE probe. We hypothesize that DPOAE components can be separated with proper phase analysis, and once separated, some of the components may have increased sensitivity to noise-induced cochlear damage. Additionally, DPOAE maps are 2D datasets amenable to analysis techniques designed for magnetic resonance imaging data (e.g. statistical parametric mapping, random field theory). We will employ these techniques to determine which approaches are most suitable for mapping data.

Specific Aim III: Determine the optimal tests for detecting noise-induced hearing loss.
Hypothesis: Recent studies suggest that some tests used to assess central auditory function may also be useful for detecting noise-induced hearing loss. As part of our work in hearing loss in HIV, we have developed a robust gap detection test that has been used successfully in the developing world to assess temporal processing. Additionally, we have experience in developing speech-in-noise tests. For this aim we will add gap detection testing and speech detection in noise to our assessment protocol after noise exposure, and compare these results to other tests (audiometry, DPOAE L/P mapping). We hypothesize that these tests may provide additional and/or complementary information about hearing damage due to noise.

Methods
We have studied 30 subjects on the repeatability protocol. The first visit included a computer-based health history and hearing questionnaire, otoscopic exam, cerumen removal, custom probe molding, wide-band tympanometry, DPOAE L/P maps, DPOAE I/O functions, gap detection, HINT, high-frequency threshold audiometry, and the fixed-level frequency threshold (FLFT) test. The FLFT test is a quick assessment of the highest audible frequency an

individual can hear at a set level (80 dB in this case). Data were collected over the course of at least 4 visits. Each visit was separated by at least 1 week. The same data were collected at each follow up visit, except that the high-frequency audiometry was limited to the sensitive region for ototoxicity (SRO) frequencies determined in the initial session.

Three additional subjects were tested on the ototoxicity protocol this year. These individuals had the same measurements described above (except FLFT at 100 dB) done prior to receiving cis-platinum, and then weekly thereafter. Thirteen subjects were tested on the noise exposure protocol. These subjects had the measurements listed above (except for the SRO) twice before, and once immediately after, a day after and a week after noise exposure.

Fig.1. Repeatability of DPOAE maps. This figure shows DPOAE level maps repeated 5 times over 2 months. The maps are highly repeatable in this case. These data provide the baseline data needed to assess when a change in a map is significant.

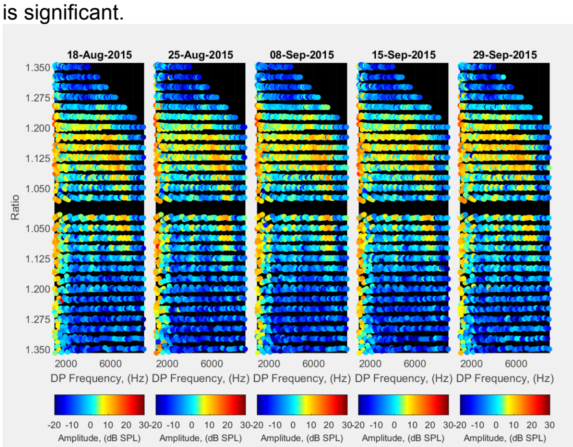
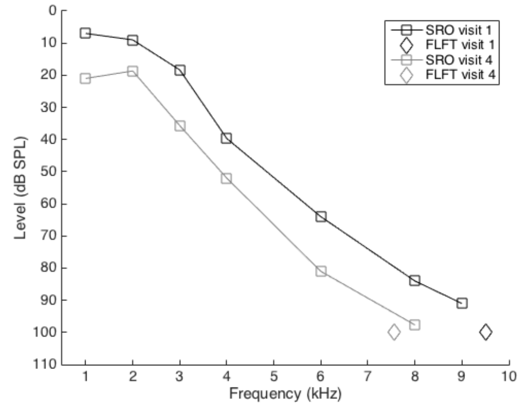


Fig.2. SRO and FLFT audiometry in a patient receiving cis-platinum. This figure shows fixed frequency audiometry results at SRO frequencies (lines), and the highest audible frequency at 100 dB from the FLFT (diamonds). The FLFT and fixed-frequency audiometry results correlate well, and the FLFT takes only 30 seconds or less to complete.



Results

a. Completed repeatability testing on 31 subjects, creating a large, unique dataset on the repeatability of DPOAE maps (see example in Figure 1), high frequency Békésy-style fixed-frequency audiometry, and the FLFT test.

b. Evaluated the repeatability and accuracy of the FLFT and submitted paper with the results (sample shown in Figure 2). The FLFT is a short, noise-tolerant, test that is amenable to administration by non-audiologists.

c. Developed statistical hypothesis test to detect cochlear changes from DPOAE maps: 1) characterize normal session-to-session variability from repeated measurements of normal-hearing subjects; 2) use random field theory to assess if session-to-session change for specific subject is within normal variability.

d. Tested 3 additional subjects on the cis-platinum ototoxicity protocol and 8 on the noise-exposure protocol.

e. To increase sample size on the ototoxicity protocol, obtained approval to test patients receiving radiation therapy, in addition to those receiving cis-platinum.

f. Worked with the Naval Medical Center San Diego to establish a relationship with Camp Pendleton to allow for testing in Marine recruits receiving firearms training.

Notes:

Status: ONGOING

MIDDLE EAR MUSCLE CONTRACTION PROJECT

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Background

The middle ear reflex is a bilateral contraction of the stapedius and tensor tympani muscles in response to high-level stimuli. Contractions of these muscles alter the impedance of the middle ear system and are expected to convey additional protection from impulse noise. MIL-STD-1474D and its ascendants (e.g., Coles et al., 1967) presume that the reflex attenuates impulses exceeding 200 ms (CHABA, 1968, p. 6). The Auditory Hazard Assessment Algorithm for Humans (AHAAH) model incorporates the middle ear reflex as an integral component of the cochlear model (Price and Kalb, 1991). The AHAAH model allows the user to calculate exposure assessments with the middle ear reflex in a contracted condition or as a consequence of an eliciting stimulus.

Although middle ear muscle contractions (MEMC) are expected to play a role in both the MIL-STD-1474D and AHAAH, approaches for characterizing auditory risk from impulse noise, the static and the dynamic properties of MEMC activated by gunfire are not well known. Voluntary and/or anticipatory contraction of the middle ear muscles is possible (Burns et al., 1993; Marshall et al., 1975), but these phenomena might not be sufficiently common or reliable to justify inclusion in risk criteria intended for application to a large population, and attempts to condition the contraction using auditory stimuli have not been successful (Bates et al., 1970; Yonovitz, 1976). The reflexive response to tonal stimuli begins adaptation almost immediately among listeners with normal hearing, and more rapid adaptation can be expected for high-frequency activating signals (Wilson et al., 1978), so it is possible that reflexive contractions elicited by preceding short-duration impulses may have minimal duration and correspondingly minimal effects on transfer of subsequent impulses through the middle ear. The proposed study includes an assessment of the role of the acoustic reflex as a mediating factor in auditory risk from small arms blast noise and this assessment will provide information concerning how MEMC can be best considered when estimating risk from small arms blast noises.

Of particular interest to the current study is the validity of the implementation of MEMC in the AHAAH model. AHAAH has been proposed as the standard damage-risk-criterion (DRC) used in the US Department of Defense (e.g., Amrein & Letowski, 2012). Peer reviews of AHAAH have identified its treatment of the middle ear as a point that requires clarification and validation.

Objectives

The specific aim of the proposed project is to inform the Office of Naval Research (ONR) and the broader scientific community about how to represent middle-ear muscle contraction (MEMC) in damage risk criteria (DRC) for impulse noise. This aim will be met by a set of studies designed to

1. Determine the probability of detecting, magnitude, and latency of impulse-elicited reflexive MEMC in the adult population;
2. Identify whether it is likely that MEMC can be elicited in most people by non-acoustic stimuli and through conditioning;
3. Identify whether it is likely that early MEMC can be elicited for individuals who are or are not warned that the sound of a gunshot is imminent.

Methods

We propose to detect MEMC via changes in the sound reflected from the eardrum. A band limited click stimulus is used as a probe, and the sound waveform in the ear canal before the introduction of a MEMC-eliciting stimulus is compared with the sound waveform in the ear canal after the eliciting stimulus is presented. In cases of MEMC-eliciting stimuli, the eliciting stimulus will be presented to the opposite ear, which is acceptable because MEMC are bilateral.

The number of participants recruited is based on a power calculation to determine 95% confidence that 95% of the population will exhibit MEMC in each condition. The minimum number of subjects required to reach 95% certainty of 95% prevalence ($N_{95,95}$) is 59, and this number is obtained if one or more subjects fail to demonstrate MEMC in a given test condition. With an $N_{95,95}$ of 59, a single failure to exhibit MEMC is sufficient to ensure that we will have less than 95% confidence that 95% of the population exhibits MEMC in that test condition. Therefore data collection for that condition will be terminated once it is determined that any participant failed to exhibit an MEMC.

Results

In FY 14, Western Michigan University (WMU) was awarded a contract to develop the Manual of Procedures for the project. The MOP describes recruiting requirements, enrollment procedures, measurement equipment and experimental procedures. In FY15, a contract was awarded to Western Michigan University to complete the measurements with human subjects. The contract has two options that will allow the WMU to test 29 subjects in 2015/2016 and 30 subjects in 2016/2017.

The WMU researchers have completed testing 6 subjects through the qualification and testing conditions. Subjects are recruited based upon their hearing levels and they must have MEMC responses that are measurable with the Interacoustics Titan platform. Subjects are evaluated with five conditions: 1) Attended visual stimulus, 2) Attended auditory stimulus, 3) Distracted unattended auditory stimulus, 4) Distracted unattended auditory stimulus with muscular activation of a button, and 5) Distracted unattended auditory stimulus with muscular activation of a realistic trigger pull. The final year of the contract for data collection will be funded.

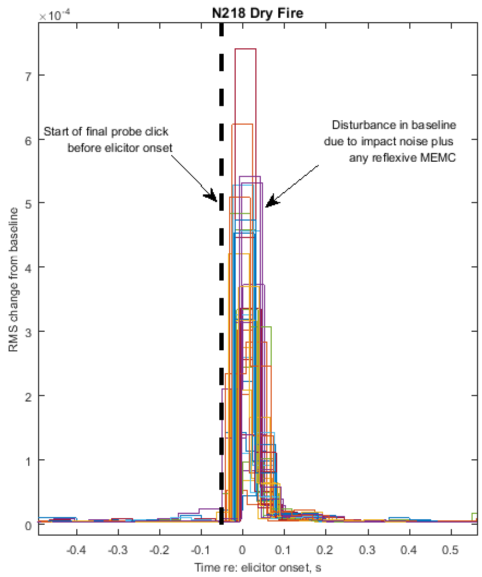

Figure 1. Changes in acoustic energy developed in the ear canal as a function of time relative to disabled gun hammer impact noise.

Preliminary results of the Dry Fire conditioned task have been obtained for the three participants (N105, N118, N218) who have completed the protocol. An example of these results is provided in Figure 1. In this figure, time=0 represents the approximate time of arrival of the DF hammer impact at the participant's ear, based on the approximate path length difference between the hammer and ear versus the hammer and field microphone. The vertical axis is the RMS difference from baseline as a function of time. Each step function represents one trigger pull. The thick dashed reference line is placed at time = -0.05, which is the beginning of the first probe click epoch that could include the acoustic hammer impact.

The change in the energy developed in the ear canal is evaluated in 50 ms intervals because the click interval is 50 ms, hence the data are plotted with a stairs plot. Thus, if the energy in the ear canal increases at any point during the 50 ms interval, the stair for that entire interval is increased. The MEMC detection paradigm is based on changes in acoustic energy in the ear canal, whether it is because of a change in middle ear impedance or because of a change in the noise (i.e., the hammer impact) infiltrating the ER-10x probe. So some stairs appear to go up at -0.050 sec, but that is not surprising. The hammer impact noise is likely to have been transmitted through the ER10x probe at the tail end of the prior 50 ms interval.

Disclaimer

The views and the opinions expressed within this paper are those of the authors and do not represent any official policy of the Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health.

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Notes:

FORWARD-PRESSURE LEVEL CALIBRATION IMPROVES RELIABILITY OF PURE-TONE AUDIOMETRY

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Background

Technology used in today's hearing conservation programs (HCPs) does not take advantage of newer objective and pre-clinical measurements of middle-ear and inner-ear status. Pure tone audiometry (PTA) currently employed in HCPs can be highly variable above 2-3 kHz and is insensitive to the early stages of noise-induced hearing loss (NIHL). PTA is conducted using headphones or earphones with a coupler (average ear) calibration. Deviations in individual-ear acoustics from average affect test validity, and variations in probe insertion or headphone placement affect test-retest reliability.

Using a standard otoacoustic emissions probe, containing a microphone and loudspeaker, an in-the-ear calibration may be performed for each insertion. However, if the stimulus level is set according to the probe microphone pressure, acoustic standing waves in the ear canal cause stimulus level errors at the eardrum as large as 20 dB above 4 kHz, depending on probe depth. Forward pressure level (FPL) calibration removes these errors, and reduces variations due to probe angle. By incorporating FPL calibration, the reliability of PTA at high frequencies can be improved, allowing for better monitoring of hearing status over time.

Objectives

The objective of this project was to develop a flexible, all-in-one clinical system (OtoStat-HCP) for military HCPs, using state-of-the-art hearing science and technology. This system includes assessment of middle-ear function, PTA, and otoacoustic emissions testing.

The objective of the current option period was to incorporate FPL calibration to improve test validity and reliability for PTA and OAE, validating the method through a series of experiments. The key performance indicators for the PTA experiment were average intrasubject reliability, which must be within 3.1 dB at 1 kHz, and test efficiency, with each threshold obtained within 40 seconds. Additional software objectives included adding the ability to compare tests to detect significant change, and ensuring a user-friendly interface and personnel database.

Methods

We compared automated PTA conducted using a standard audiometer in common use in HCPs (Benson CCA-200mini + TDH-39P headphones) to our FPL-calibrated prototype audiometer (OtoStat-HCP). Specifically, we analyzed how much difference FPL calibration makes to test-retest reliability and significant threshold shift criteria.

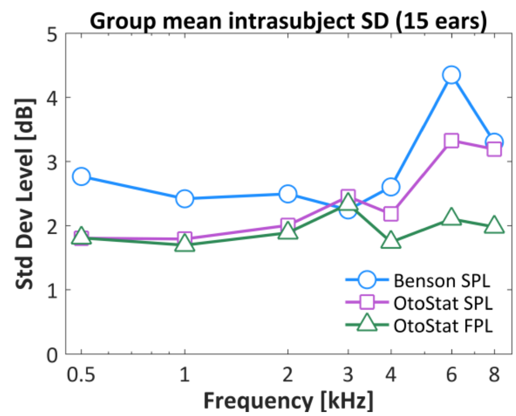

Fig.1. Audiogram reliability. Mean intrasubject variability at each test frequency for the Benson audiometer (blue) and the OtoStat is shown for two calibration methods: in-the-ear dB SPL (pink) and in-the-ear FPL (green). Only FPL calibration met the benchmark across all frequencies.

Fifteen subjects completed the study. The PTA test procedure was similar to those commonly used in HCPs, using pulsed-tone test frequencies at 0.5, 1, 2, 3, 4, 6, and 8 kHz, and an automated modified Hughson-Westlake audiometric procedure.

Each of 10 trial-pair blocks consisted of one test on OtoStat and one test on the Benson audiometer. The order was randomly determined for each block. After each audiogram, the earphone or headset was removed from the participant and refitted. The tester was instructed to achieve a good fit or placement, but was not asked to achieve either an identical or different fit to previous blocks. A foam earplug was placed in the contralateral non-test ear.

Results

As shown in Figure 1, both audiometers met the benchmark of 3.1 dB at 1 kHz, but OtoStat with FPL calibration was the only method that met the benchmark across all frequencies, including 6 and 8 kHz. On average, thresholds were obtained well within the 40s benchmark.

Figure 2 shows that when translating the intrasubject reliability into statistically-derived significant threshold shift (STS) criteria, shifts of 15 dB are reliably detectable at all frequencies, including 6 and 8 kHz, if FPL calibration is used. In comparison the standard audiometer with a coupler calibration is worse at higher frequencies, with shifts of 20 to 25 dB needed for statistical reliability.

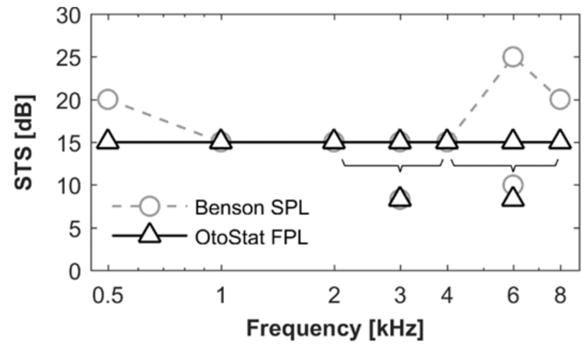

Fig.2. Comparisons of statistically-derived STS criteria using intrasubject standard deviations. Benson audiometer (dB SPL; light gray circles with dashed lines), and OtoStat with FPL calibration (black triangles with solid lines). The symbols below the braces indicate the average STS criteria over 2, 3, and 4 kHz and 4, 6, and 8 kHz

It has long been a limitation in HCPs that PTA testing above 4 kHz has not had sufficient reliability to enable the detection of the early stages of NIHL. Our results indicate that test-retest reliability is better with FPL calibration and that the improvement is clinically meaningful, potentially allowing HCPs to have more confidence in determining significant threshold shifts at 6 and 8 kHz - key frequencies for early detection of NIHL.

Notes:

Status: Ongoing

HEARING LOSS AND SIGNIFICANT THRESHOLD SHIFTS IN US NAVY SUBMARINERS

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Background

Hearing loss is a common disability in Navy personnel and a very expensive burden on the VA system. A study of hearing conservation program data from 1979-1982 estimated the prevalence of hearing loss, measured as a significant change in hearing threshold, in submariners at approximately 20%. A 2005 CNA report examined the relationship between hearing loss and length of service aboard specific types of ships for enlisted personnel. Time spent assigned to submarines in occupational ratings that involved working near engines or loud machinery did not significantly change risk of STS compared to time spent assigned to shore duty. Conversely, time assigned to submarines while in other occupational roles was associated with increased hearing loss. This report recommended follow-up longitudinal cohort studies within and across ship classes, as well as a study of officers. Therefore, our analyses used data from the Submariner Epidemiology Research Program (SERP), the Navy's first dedicated submariner longitudinal cohort study, to examine hearing loss in the Submariner Force, both for enlisted personnel and officers.

Objectives

The objectives of this study were to determine the baseline prevalence and cumulative incidence for hearing loss (HL) in the submariner population, to determine incidence of significant threshold shifts (STSs) in the submariner population, and to identify risk factors for STS in submariners

Methods

This was a retrospective cohort study examining hearing loss (HL) and significant threshold shifts (STSs) in submariners. Only sailors whose first assignment to a submarine occurred between 2004 and 2014 were included in these analyses.

The two outcomes of interest, HL and STS, were assessed using audiogram data from the Defense Occupational and Environmental Health Registry System – Hearing Conservation (DOERHS – HC) data repository (data available from January 1, 2004 to May 14, 2015). Hearing loss was defined as any frequency-specific threshold greater than 25 decibels (dB), at the 2kHz, 3kHz, or 4kHz frequencies. A STS was defined according to the OPNAVINST 5100.19E and OPNAVINST 5100.23G as an average 10dB or greater change between audiograms, using data at three frequencies (2 kHz, 3 kHz, and 4 kHz) in either ear. To remove the possibility of a temporary shift, Navy policy traditionally requires 2 additional audiograms within 90 days of the first audiogram showing a shift, in order to confirm that this represents a permanent shift. Typically, after three audiograms in 90 days with evidence of a shift, a new baseline (termed a "re-established baseline") audiogram is recorded in the DOERHS – HC data repository. For our analyses, we confirmed STS status in two ways. First, if a submariner had an audiogram labelled as a "re-established baseline" after first assignment to a submarine and that audiogram represented a positive shift (decrement in hearing compared to the most recent reference audiogram), then he was considered a STS case. Alternatively, if a submariner had 3 sequential (non-baseline) audiograms that occur within 90 days of each other that all have evidence of a positive shift compared to the most recent reference audiogram, this was also considered a confirmed shift, even if the individual had no record of a subsequent re-established baseline. Any HL or STS that occurred more than 30 days after starting submarine service was considered an incident case. Submariners with hearing loss at the time of entry into submarine service were excluded from HL incidence calculations.

Both cumulative and stratified rates of STS and HL were calculated. Demographic and military factors, including age, race, marital status, education, rank/paygrade, occupational role, and career history of assignments were examined as risk factors. Crude hazard ratios and 95% confidence intervals (CI) were calculated for these factors using Cox proportional hazards regression.

Results

There were 19,063 submariners included in our initial HL study population. Of these, 766 were found to have hearing loss at the time they joined the submarine service (4.0%). After excluding these baseline cases, we found 1,395 submariners (8.3%) developed hearing loss, yielding an incidence rate of 21.3 cases per 1,000 person-years (95% CI 20.2, 22.5).

Among enlisted submariners, there were 1,289 HL cases, with an incidence rate of 22.7 cases per 1,000 person-years (95% CI 21.5, 24.0).
Among officers, there were 106 HL cases, for an incidence rate of 12.2 cases per 1,000 person-years (95% CI 10.0, 14.8). For both officers and enlisted, those in the oldest age groups had the highest rates of HL. Incidence rates were not significantly different by paygrade/rank. While no significant differences in HL rates were observed by occupational role for officers, incidence rates for all Machinist's Mate occupational ratings were significantly higher than those of most other occupational ratings that were examine. Interestingly, there was a trend of decreasing HL rates observed for those with increased time assigned to submarines for both officers and enlisted. Finally, enlisted submariners who had a history of ever being assigned to a surface ship had an increased rate of HL, but no such difference was observed for officers.

There were 19,029 submariners included in our STS study population; among these, we identified 602 submariners (3.2%) who experienced a total of 608 shifts, yielding an incidence rate of 8.6 cases per 1,000 person-years (95% CI 7.9, 9.3).

Among enlisted submariners, there were 519 individuals who experienced at least one STS after joining the Submarine Fleet, with 513 experiencing 1 shift and 6 experiencing 2 shifts, for a total of 525 shifts. This resulted in an incidence rate of 8.6 STS cases per 1,000 person-years (95% CI 7.8, 9.3). Among officers, there were 83 individuals who experienced a STS after joining the Submarine Fleet, with no officers experiencing multiple shifts. This resulted in an incidence rate of 8.9 STS cases per 1,000 person-years (95% CI 7.1 11.0).

Again, for both officers and enlisted, those in the oldest age groups had the highest rates of STS. Additionally, both enlisted sailors and officers who entered submarine service at a higher paygrade or rank had a higher rate of STS. While no significant differences in STS rates were observed by occupational role for officers, incidence rates for Electronics Technician (NUC), Machinist's Mates (AUX), and Machinist's Mates (WEP) were significantly higher than the two enlisted occupational ratings with the lowest STS incidence rates, Culinary Specialists and Missile Technicians. For both officers and enlisted, those with less than 2 years of service on submarines had the highest rate of STS. Finally, those who had a history of ever being assigned to a surface ship had an increased rate of STS compared to those who had never been assigned to a surface ship

Using Cox proportional hazards regression to account for time to first STS, we examined unadjusted hazard ratios to determine a submariner's risk at any given time point of experiencing a STS. These analyses found similar patterns as observed for the stratified rates. Older age, higher rank, less time assigned to submarines, and a history of assignment to surface ships were all associated with increased risk of STS. Among enlisted, CSs and MTs were at lower risk of STS, while ET(NUC)s were at higher risk of STS. Among officers, those who worked in the executive department on the submarine were at greater risk of STS. However, certain variables, particularly time assigned to submarines, violated the proportional hazards assumption underlying the models, an issue which will need to be addressed in the final adjusted models.

Notes:

Status: Ongoing

CONCERNS REGARDING USING MIL-STD-1474E "NOISE LIMITS" AS A HEALTH HAZARD ASSESSMENT TOOL

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Background

MIL-STD-1474D “Noise Limits” has been replaced by MIL-STD-1474E which includes the Auditory Hazard Assessment Algorithm for Humans (AHAAH) as one method for evaluating risk of hearing injury from exposure to impulsive noise. MIL-STD-1474E is a set of design criteria (i.e., an acquisition standard and “is neither a hearing damage risk criterion nor a hearing conservation criterion,” (MIL-STD-1474E, p. ii). However, there is an effort afoot to approve an ANSI standard (ASA S3/WG62) allowing the AHAAH to be used for health hazard assessments (HHA).

Several authors have argued that the previous methods used for hearing injury HHAs (i.e., MIL-STD-1474D) should be relaxed, permitting Servicemembers to be exposed to more energetic impulsive noises. For example, Chan et al. (2001) analyzed the Albuquerque blast overpressure data set (e.g., Johnson, 1993) and suggested that the limit should be raised by 9.6 dB. Amrein and Letowski (2012) argue that the AHAAH model is the best method for predicting the risks of hearing injury from exposure to impulsive noise and note that “Failure to do so indicates a lack of leadership in the scientific and medical communities of the U.S. Army, both of whom are responsible for the survivability and lethality of its Soldiers,” p 32).

In spite of these recommendations, there is ample evidence to the contrary. If the current HHA method is overly conservative, one would expect that Soldiers should be sufficiently protected from impulsive noises. Ahroon et al., (2011) analyzed the Defense Occupational and Environmental Health Readiness System – Hearing Conservation (DOEHRS–HC) for the hearing status of enlisted Soldiers in 32 military occupational specialties (MOS) over the years 1998 through 2007. The results revealed that only one MOS (18B, Special Forces Weapons Sergeant) showed H-1 hearing profiles for only 2005 (see Fig 1). Thus, why relax the standard if we are not protecting at least 95% of Soldiers?

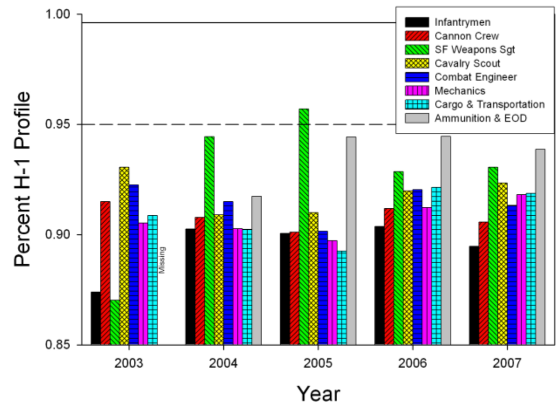

Fig. 1. Percentage of H-1 hearing profiles for military occupational specialties for years 2003-2007 (from Ahroon et al., 2011)

Objectives

The objective of this project is to fully document the effects of acoustic impulses on the middle ear and on middle-ear muscle contractions (MEMC). This project will provide critical information on the middle ear musculature states during warned and unwarned exposures to acoustic impulses. This information is necessary in the development of new (or revision of existing) damage risk criteria and HHA methods for exposure to high-level acoustic impulses such as those experienced by users of military and civilian law enforcement weapon systems, civilian recreational hunting and shooting, and operators of industrial equipment producing high-level impulsive noises (impacts and impulses). The technologies to be used include wide-band tympanometry and laser-Doppler vibrometry.

Methods

Acoustic Reflex (AR) Prevalence.—Data were obtained from the 1999-2012 rounds of the National Health and Nutrition Examination Survey (NHANES) (N ~ 15,000, ages 12 to 85+). Ipsilateral ARs were obtained for 1 and 2 kHz elicitors at 103 and 105 dB HL respectively (Earscan 3). The 0.5 s elicitor was presented at the beginning of a 1.5 s observation window.

Raw AR traces (F_s = 56 Hz) were imported into MATLAB® for processing via two different detection algorithms. Algorithm output was appended to an NHANES dataset containing demographic, audiometric, tympanometric, and related variables. AR prevalence was estimated using Stata (v.14), accounting for the complex sample design of NHANES using procedures recommended by the National Center for Health Statistics. Multivariable models were developed starting with univariable analyses and leading to a reduced model consisting only of significant factors after controlling other factors in the model. Reflex status was determined by the presence of at least one response in each ear.

Results

Conditioning of the AR—Price (2005) contends that individuals who "expect" an impulse are classically conditioned to activate the AR prior to the impulse. He references Simmons et al. (1959) who displayed the phenomenon in five cats, yet ignores the conclusions of Bates et al. (1970) who noted "(t)he best conclusion to be drawn from the experiment is that conditioning of the AR, if it occurs at all, is a very fragile and undependable phenomenon. *Just why this reflex should be so hard to condition, especially when it has been reported to occur in cats, is certainly not clear*," (p. 33) (emphasis added).

The literature does not support the contention that the human middle-ear reflex can be classically conditioned. Table 1 summarizes the literature on classical conditioning of the AR.

Table 1. Percentage of subjects exhibiting classical conditioning of the acoustic reflex.

Study	Ss Conditioned
Djupesland (1965)	80%
Brasher et al. (1969)	0%
Bates et al. (1970)	0%
Marshall et al. (1975)	86%
Yonovitz (1976)	80%

AR Prevalence.—The presence of an AR was defined as reflexes present in both ears for at least one of the two ipsilateral elicitors presented. In no participant group and detection approach was the prevalence of ARs greater than 88% or was the lower bound on the 90% confidence interval greater than 86%. Data for the 18-30 age group with H-1 (AR 40-501) hearing status are in Table 2.

Table 2. Estimate of AR prevalence determined to be present in each ear for at least one of two ipsilateral elicitors (from Flamme et al., 2016).

Approach	H-1 profile ages 18-30	
	Estimate	90 % CI
Either	88	[86, 89]
Frequentist	85	[83, 86]
Bayesian	75	[73, 77]
Both	72	[70, 74]

Conclusion:

ARs cannot be used in HHAs when defining the risk of hearing injuries from impulsive noise.

Work supported by the DoD Injury Prevention, Physiological and Environmental Health Award (IPPEHA) X81XWH-14-2-140 and the U.S. Army Medical Research and Materiel Command Military Operational Medicine Research Program Project 17140.

Notes:

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Status: ONGOING

Objective Comparison of Foam vs. Deep Custom-Molded Earplugs, Protective Effectiveness and User Preference, Inclusive of User Training Implications

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Background

The motivation for this research is to assist the Navy in making an objective, field application-valid evaluation of the appropriateness of foam earplugs versus deeply-molded custom earplugs for protecting U.S. Navy personnel on various decks of Navy ships where high-intensity noise exposure is at issue, with particular emphasis on aircraft carrier flight decks.

Objectives

This research entailed a comparison of slow-recovery, one-size-fits-most, foam earplugs and deeply-molded, personalized-fit, custom-molded earplugs. The hearing-protective capabilities (i.e., spectral attenuation data) of the two earplugs were obtained and compared at three stages: 1) after only printed instructions that were supplied by the manufacturer with each earplug were provided to the subject before fitting (inexperienced-subject-fit), 2) after each subject was personally trained by an experimenter (trained-subject-fit), and 3) after 21 days of daily usage following the initial trained-subject-fit, but with no additional training at the 21-day juncture. The effects of manufacturers' instructions, experimenter training, and the retention of training benefits on attenuation achieved were compared across the two earplugs.

Methods

Twenty-five subjects were pre-screened and qualified per the requirements of ANSI S12.6-2008 for real-ear-attenuation-at-threshold (REAT) testing of hearing protector attenuation. Deep ear impressions of the ear canal, around the second bend (when present and possible), were taken on all subjects by a professional audiologist. From these impressions, deep-insertion custom-mold earplugs (AegisSound CTE30X) were made. The foam earplug was the 3M Classic™ cylindrical earplug. Thereafter, 21 subjects completed the full experiment, each using both earplugs in counterbalanced ordering during the test sessions; this satisfied the ANSI S12.6 requirement of a minimum of 20 subjects. The ANSI S12.6-2008 attenuation test procedure includes both "Method B" inexperienced-subject-fit (hereafter, "untrained subject) test and "Method A" trained-subject-fit (hereafter, "trained subject") test protocols. Both of these Methods were applied to compare initial attenuation performance of the two earplugs, with Method B (untrained subject) applied first, followed by Method A (trained subject). The attenuation performance difference between the untrained subject-fit and trained subject-fit was used to compare the effects of initial training for each of the two earplug types. The average time spent by the experimenter (Dr. Lee) for training, based on what he experienced as needed with the subjects, was about 10 minutes for custom-mold earplugs and 20 minutes for foam earplugs, respectively. Thereafter, subjects were asked to use their earplugs on a daily basis for 21 days, uninterrupted. After 21 days usage, each subject returned to the laboratory for another test using the untrained subject-fit procedures of Method B. This final test, conducted on each subject with both earplugs in counterbalanced order, was performed to measure whether the effects of initial fit training was retained, and by how much for each earplug. All measurements were conducted in the REAT-instrumented reverberant room at Virginia Tech's Auditory Systems Lab, which meets the requirement for the ANSI S12.6-2008 standard. Test signals comprised seven 1/3-octave bands of pink noise centered at 125, 250, 500, 1000, 2000, 4000, and 8000 Hz. Following the post-21 day attenuation test session, a self-report rating scale was used to obtain subjects' perceptions on comfort, ease of use, quickness to fit, and perceived protection level for both earplugs.

Results

Per Figures 1 and 2, as compared to attenuation achieved after the initial untrained subject fitting condition, both the foam and custom-mold earplugs demonstrated statistically-significant improvements in attenuation at all 7 test frequencies for foam and 6 frequencies for custom-mold, after the subject fit the devices with experimenter training (trained subject). Also, before training (Figure 1), the custom-mold earplug yielded significantly higher attenuation than the foam earplug at low frequencies of 500 Hz and below; however, 3 of 21 subjects were unable to insert the custom-mold earplug prior to experimenter training, and this resulted in disparately larger standard deviations for the custom-mold device (and a lower untrained subject NRR of 5 as compared to 14 for the foam plug). After initial training by the experimenter, both earplugs achieved significantly higher attenuation over the untrained subject-fit condition, at all 7 test frequencies, for each device. Also, the custom-mold earplug retained its attenuation advantage over the foam earplug after initial training, with statistically-significant (higher) attenuation at 125 Hz (by 4.9 dB) and at 250 Hz (by 3.8 dB) (Figure 2).

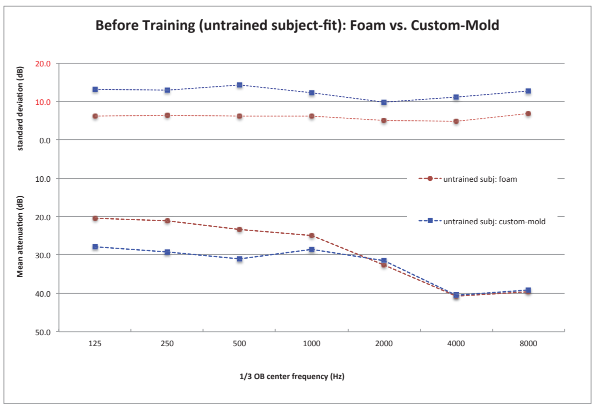

Figure 1. Attenuation of foam and custom-mold earplugs with untrained subject-fit per ANSI S12.6-2008 Method B.

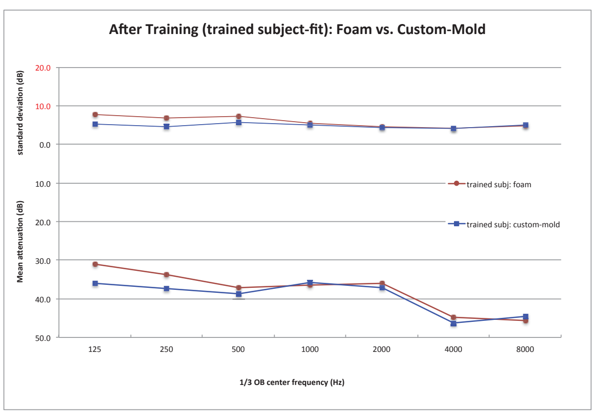

Figure 2. Attenuation of foam and custom-mold earplugs with trained subject-fit per ANSI S12.6-2008 Method A.

After 3 weeks of use following the initial training, the custom-mold earplugs were found to resist a loss of training benefit more than did the foam earplugs (Figure 3). After this period of use, with no additional training during the period, the custom-mold earplugs provided significantly higher protection at the low frequencies of 500 Hz and below (by 8.0 dB, 6.5 dB, and 5.3 dB at 125 Hz, 250 Hz and 500 Hz, respectively) than did the foam earplug, and slightly better (but not statistically-significant) attenuation at 1000 Hz and above.

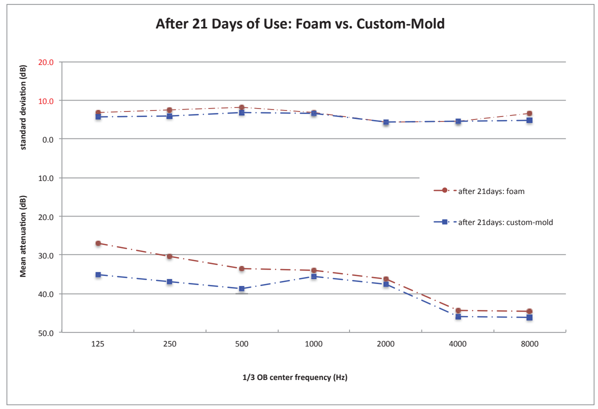

Figure 3. Attenuation of foam and custom-mold earplugs with untrained subject-fit per ANSI S12.6-2008 Method B, after 21 days of usage of earplugs following initial training session.

Finally, the rating scale results demonstrated that overall, subjects preferred the custom-mold earplug over the foam earplug for ease of use after 3 weeks of wearing it, and also rated that they could fit it slightly more quickly. While usage preference is a matter of personal choice, it can be an important factor in the tendency of a hearing protector to be worn properly and consistently.

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Notes:

Status: Ongoing

SHIPBOARD NOISE CONTROL

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Background
Warfighters are exposed to high noise levels in many routine situations which impact their work performance, communication ability, and in some cases can lead to long-term hearing damage. Reducing exposure to loud environments cannot occur by limiting where and how the warfighter does their job. The environments themselves need to be quieted through effective control methods. Techniques to reduce noise must be developed and optimized to be effective while minimizing non-acoustic impacts.

NCE has worked on developing accurate prediction tools on methods that can be applied to the entire US Navy fleet. This involves continued work to improve prediction algorithms used in the Designer NOISE® software, with a focus on areas that produce the highest noise levels. In particular, NCE has developed modeling approaches to predict and assess sound pressure and noise exposure levels on CVN during flight operations. By combining updated Designer NOISE® algorithms and models with Topside airborne noise measurements, NCE has developed accurate predictions of noise levels within compartments on the Gallery Deck. This knowledge can be used to assess tradeoffs between noise reduction and non-acoustic impacts for various treatment options.

The Navy has also identified the need for a noise exposure limit that more precisely characterizes the damage risks associated with intermittent and impulsive sounds. A-weighted sound pressure levels greater than 85 dB(A) are commonly characterized as being hazardous. However this metric alone is unable to capture the damage risk associated with the broad range of noise induced hearing loss pathologies. Developing new damage risk metrics that encompass the various noises a warfighter is exposed to would require large populations, logistical complexities, and in some cases has barriers due to restrictions on the use of human test subjects. A theoretically based model capable of correlating features of the acoustic stimuli and various noise induced hearing loss pathologies is needed. The results from this model would be used to establish damage risk criteria relevant to the noise environments Navy personnel are exposed to over a 24 hour period.

NCE has begun this work by investigating and exercising mechanical-acoustic models of the cochlea to predict basilar membrane responses to acoustic stimuli. The goal is to utilize a theoretically based model of the human ear for the purposes of relating features of the acoustic stimuli measured in Navy environments to various noise induced hearing loss pathologies. The results from this model could be used to establish damage risk criteria relevant to the noise environments Navy personnel are exposed to over a 24 hour period (i.e. steady-state, intermittent and impulsive).

Objectives
The overall objective is to review USN approach to noise control, including criteria, specification development, and implementation of an effective Noise Control Plan. As part of this effort, NCE is working to develop tools that can be used to assess and develop effective noise control approaches on all Navy platforms while minimizing non-acoustic impacts.

NCE is also working to gain a better understanding of hearing loss and hair cell damage mechanisms, and how the ear responds to loud steady-state and impulsive sounds. The results of these efforts can be used to set goals for noise levels in areas frequented by warfighters and to set limits for new and existing constructions.

Efforts on some tasks have been halted at the suggestion of the COTR; these include development of Return-on-Investment software and further testing of treatment effectiveness.

Methods
NCE is evaluating various updates to *Designer NOISE®* core algorithms to improve overall performance and accuracy, particularly with respect to new Naval aircraft. NCE is also

assessing acoustical effectiveness algorithms using available data on new outfitting and treatments. Noise exposure calculations have been incorporated in the software.

NCE has undertaken significant efforts on developing accurate models of CVN noise and exposure levels. These efforts have utilized measurement data from previous years combined with new approaches to modeling in *Designer NOISE*®.

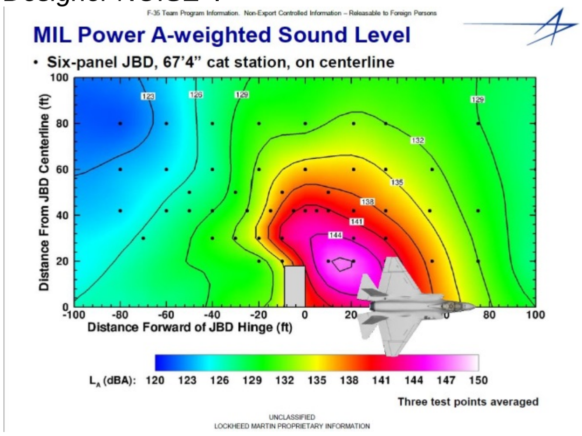

Fig.1. F-35 noise contours measured at the Edwards Air Force Base air field

Efforts to develop a 24-hour Time Weighted Average exposure limit has led to development of models of basilar membrane and hair cell motion within the inner ear. Understanding causes of outer hair cell damage are important to the development of appropriate steady state and impulsive noise criteria.

Kurtosis has been shown to correlate with the increased hazard that high intensity acoustic transients pose compared to steady-state noise. However, analysis of data collected on CVN's demonstrated the kurtosis of an acoustic stimulus is sensitive to the time-scale over which the kurtosis value is calculated. Future work can include investigations into the applicable time scales relevant for kurtosis enhanced damage.

Efforts on some tasks have been halted at the suggestion of the COTR; these include development of Return-on-Investment software and further testing of treatment effectiveness.

Results

Significant progress has been made in developing tools that can be used to assess noise and exposure on existing and future Naval platforms. *Designer NOISE*® has been shown to produce accurate predictions of noise and exposure levels on CVN during flight operations. This tool can be used to assess potential treatments and approaches for noise reduction.

Initial models of the cochlea and basilar membrane show promise to further understanding of hearing mechanisms and damage of the outer hair cells. These initial efforts have helped to identify the path for future work.

Future work includes measurement, assessment, and modeling of Joint Strike Fighter on LHA. NCE will continue efforts to improve *Designer NOISE*® algorithms and methodologies, and will continue efforts to develop models of hearing response and damage.

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Notes:

Status: Ongoing

NOISE INDUCED HEARING LOSS RESEARCH FOR MILITARY AND POWERPLANT APPLICATIONS

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Background

Navy personnel work and live in noise levels that put them at risk for noise induced hearing loss (NIHL) and tinnitus. The overall objective of this project is to identify and improve solutions to reduce the Navy's risk for NIHL/tinnitus and to extend this technology to other government agencies. This effort is part of ONR's Noise Induced Hearing Loss Program, which is directed towards identifying approaches for reducing noise exposure and hearing loss through the use of innovative acoustic materials and noise control methodologies. Recently, the US Department of the Interior, Bureau of Reclamation (Reclamation) has noticed an increase in disability claims for NIHL and tinnitus suggesting that their workers are also at risk. Because of this, Reclamation has decided to team with ONR, as part of this program, to research how technologies being developed for the US Navy can be leveraged for applications in their powerplants. The effort this year has been to (1) research and implement ways to leverage advanced noise control technologies that have been developed in existing programs for use in hydroelectric powerplants and (2) develop and adapt other technologies for noise control, such as active noise control, for industrial use. The effort is a partnership between ONR and reclamation.

Objectives

The major objectives of this year's efforts were the following:

- Finish quantifying noise levels in a number of hydroelectric powerplants and research methodologies of transferring novel technologies for use in noise mitigation designs.
- Validate novel measurement techniques, including the use of acoustic array and focalization technology, to accurately determine noise sources in a complex noise environment.
- Based upon the results of the measurement phase, develop and implement noise control strategies and validate results for selected facilities.
- Investigate the use of other advanced noise control techniques, such as active control and spray-on damping, for use in the powerplant environment.

Methods

Methodology included conducting a series of acoustic and vibration surveys in all areas of eighteen powerplants which included very large plants such as Hoover Dam (Nevada) and Shasta (California). Measurement techniques included the use of acoustic array technology that features a 3D solid sphere acoustic "camera" to capture sound pressure levels (Figure 1).

Fig.1. Typical acoustic array setup in a powerplant

The specialized software algorithms then utilize focalization and transformation matrix algorithms to localize the sources of noise and process the data so that hots spots can be visually portrayed (Figure 2).

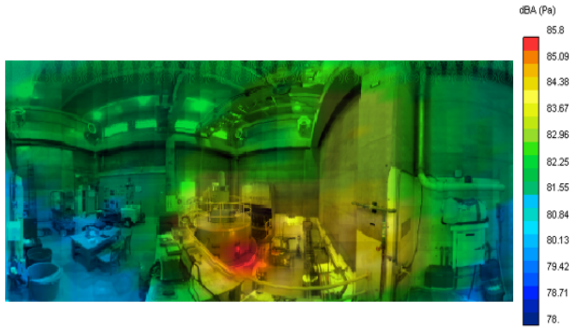

Fig.2. **Acoustic array measurement results showing hot spot emanating from generator cooling slot**

The measurement process results in information that is used to develop comprehensive noise control plans incorporating technology developed through previous US Navy SBIR programs such as spray-on damping, along with other noise control techniques. These plans are reviewed with Reclamation subject matter experts and plant managers to select facilities in which to implement controls.

The use of active noise control (ANC) technology to create zones of silence is also being investigated as part of this effort. In a high noise environment where it may not be feasible to sufficiently reduce levels, the creation of localized “zones of silence” around workstations will reduce exposure to workers. Based on the noise surveys conducted, a candidate location at the Grand Coulee Left Powerhouse Compressor Room was selected to design and implement this (ANC) technology. A proof-of-concept ANC design will be developed and a prototype system tested to determine the effectiveness of this technology to reduce the noise exposure to personnel working at this location.

Results

Acoustic and vibration data was collected at a total of 18 hydroelectric power generating facilities. The acoustic data included the use of advanced experimental techniques using an acoustic array that employs focalization algorithms. It was verified that this technique was able to identify the primary noise sources and to rank them in order of importance. The results of this experimental research was used to develop optimized noise control plans which incorporated advanced materials and techniques such as spray-on damping material. These plans were reviewed with Department of Reclamation technical experts. As a result of this effort, several plants were chosen to have these noise reduction plans implemented. The facilities include Grand Coulee Left Powerhouse, Shasta Powerplant and Flaming Gorge Powerplant. Materials have been delivered to Grand Coulee and are awaiting installation. Installation at the other two facilities will be accomplished in the upcoming fiscal year as well as the verification of effectiveness through measurements.

Advanced noise control (ANC) techniques using active noise reduction has also been investigated and two potential locations for demonstration have been identified. Development of the ANC algorithms has been started and a demonstration of using ANC to create quiet zones around workstations is targeted for next fiscal year.

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LONG-TERM PERFORMANCE OF HEARING-PROTECTIVE CUSTOM-MOLDED EARPLUGS

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Background

Navy ships can be noisy places, even in the sleeping quarters. Unlike most civilian jobs, 24-hour noise exposures must be considered. In summer, 2008, NAVSEA purchased a suite of custom-molded earplugs for the commissioning crewmembers of a new, and very noisy, Navy ship, USS Freedom, LCS-1. The Naval Submarine Medical Research Laboratory (NSMRL) was tasked to provide technical and audiological monitoring of the LCS-1 crews, and saw the opportunity to implement and objectively evaluate ideas for advanced hearing-conservation programs (HCPs).

The intervention had multiple components:
a) Audiometry with in-depth follow-up of any hearing shifts
b) Custom-molded earplugs fit and overseen by research team
c) Wide array of standard hearing-protection devices (HPDs) issued
d) HPD attenuation measured
e) Personalized HCP training
f) Collaborative evaluation with the crew of all HPDs and all other program elements
g) Feedback to the crew, as individuals and as a group, as progress unfolds (updates on their own data, for their workgroup, and for the ship as a whole)

Is this approach to Navy hearing conservation successful? The success of this program has not yet been systematically evaluated.

Objectives

Conduct a longitudinal study evaluating the deployment and use of custom-molded hearing protection and enhanced hearing-conservation measures on the LCS-1 crews. Follow the original sailors for at least 5 years. Additionally, study the attitudes and custom earplug attenuation of submarine crews over periods of time. The eventual goal is elimination of noise-induced hearing-threshold shifts in these crews.

Methods

Follow up on hearing levels will use annual audiograms from the Defense Occupational and Environmental Health Resource System (DOEHRS) database. Changes will be placed in one-year follow-up categories. Hearing level changes will be compared to the sailor’s first contact with the NSMRL team and custom HPD fitting.

The rate of hearing shifts among the LCS crew will be compared to rates on other ships by reference to published studies; and to a specific contemporary small combatant (DDG) crew whose hearing records will also be obtained from DOEHRS.

Attenuation measurements will use the Real-Ear at Threshold (REAT) technique, using the Kevin Michael system. That measurement compares the softest sounds barely heard by an individual with and without the earplug in place. For comparability, attitudes will follow many of the same survey questions used during the prior study.

The submarine study will provide shorter term information on custom HPD performance. We will outfit selected crewmembers with the HPDs before a modest (weeks to months) deployment and re-contact them after their return. HPD attenuation will be re-measured with REAT, and a questionnaire will assess their subjective reactions to various aspects of HPD use.

Results

Follow-on audiograms of FREEDOM's crew became much less numerous over barely 3 years, as crewmembers transferred to other duty and separated from active duty. Since the varied (and largely unknown) noise exposure of crew after leaving the ship was substantial, this study concentrated on hearing shifts that occurred while still onboard FREEDOM.

Shifts are termed "significant" (STS) based on a decrement of 3 frequencies. They are further categorized as Temporary (TTS) or Permanent (PTS) depending whether a follow-up test confirms the decrement.

Annual new cases of STS as a fraction of the onboard population are plotted in the Figure. There is no specific pattern of a change over time evident, and the uncertainty of small samples overcomes any specific difference.

For a best estimate of overall incidence, the number of new onboard STS cases were compared to the number of remaining onboard crew (minus those with a prior STS). That ratio is 7 over 149 man-years at risk onboard; or 4.7% (95% confidence range of 1.9 to 9.4%)

Is ~5% per year higher or lower than other shipboard exposures? Most existing reports only have a "snapshot" of one point in time, without accounting for individual sailor's years at risk. So a report like "20% of that year's crew audiograms show a shift" is of no comparative value.

One prior NSMRL study on an aircraft carrier deployment was appropriately longitudinal in nature. An incidence of 4.4% PTS per person-year exposed over that period was observed. Thus the carrier and LCS rates cannot be statistically distinguished from each other. Adding to the LCS uncertainty is the fact that some shifts were only temporary, and that at least one false positive shift was found - strongly suggesting the presence of a spurious "shift" in the other direction. So the LCS-1 incidence of PTS is most likely below 3%.

For a more focused comparison, we obtained serial audiograms from the crew of USS STERRETT (DDG-104), a destroyer also commissioned in 2008. We analyzed the data, using methods as close as possible to the methods used for the LCS-1. The results will be available at the Program Review presentation.

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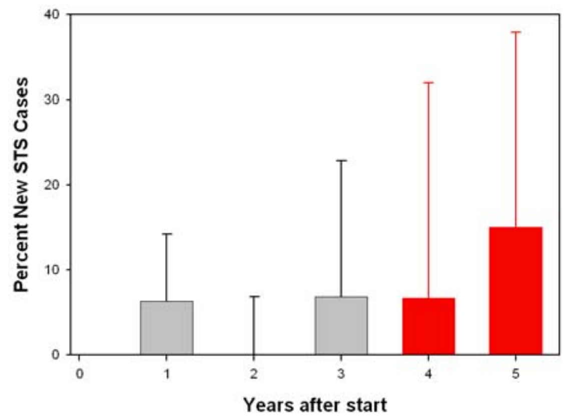

Figure. Annual incidence of new STS cases, on LCS-1 with error bars showing the upper 95% confidence limit due to random sampling error. The red bars indicate STS cases occurring in sailors no longer on FREEDOM. The lower 95% confidence limit bars are not shown, but are below 4% in all five years.

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Notes:

Status: Ongoing

INNOVATIVE DIVE HELMET COMMUNICATION SYSTEM

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Background

Helmeted divers frequently have difficulty communicating among themselves and with the surface due to out-dated equipment and background noise, directly impacting diver safety and effectiveness. Diver feedback is universal that existing communications impair their ability to complete their mission. Sound quality is low; there is significant interference from regulator operation, tools, and environmental noise. Significant feedback exists due to a lack of speaker and microphone isolation, and changes in gas density shift voice resonant formants resulting in reduced intelligibility. Beyond anecdotal diver reports of communication difficulties many studies have documented the interference of communications due to high noise levels generated by the helmet, tools, hyperbaric chambers, vessels, and other equipment (Wolgemuth, 2008; Evans 2007; Knafelc, 1997; Anthony, 2009; Parvin, 2003). Noise levels inside a Mk-21 dive helmet can reach sustained levels over 100dB (A). A human-factors study by the Navy Experimental Dive Unit comparing the KM 37 to the MK 21 found "Noise Level and Communication" was even worse in the newer KM 37 than in the old MK 21 (Anthony, 2009). Currently, divers will often skip-breathe during communications to be able to hear the incoming audio. The existing system is further hampered by fragile low quality components.

To improve communications with helmeted divers, Triton Systems, Inc., in collaboration with our team, will refine the improved communication system developed in Phase I. Initial testing has demonstrated improved intelligibility in both receive and transmit communications as well as reduced noise exposure, offering increased warfighter effectiveness. Triton's system provides superior intelligibility vs. other options. The system is a low-cost, drop-in replacement for the current communication system that does not require batteries, additional electronics, new umbilicals, etc.

Objectives

- Refine Phase I form factor
  - A Gen II design will be fabricated to achieve further performance improvement
- Assess system robustness
  - The system will be tested for robustness to ensure survival in the harsh diving environment
- Demonstrate improved communications in both benchtop and underwater laboratory environments

Methods

During the Phase I period, Triton engineers visited the Naval Submarine Medical Research Laboratory (NSMRL) both to review and confirm system requirements as well as to demonstrate final breadboard prototype effectiveness. In discussions with Navy divers, the team reviewed several system designs (including improved transducers, active noise reduction, DSP improvements, etc) for increased intelligibility and reduced noise and downselected to an optimal design. During the second visit, the divers tested Triton's full system versus the legacy system and were impressed with the communication intelligibility improvement provided by Triton's breadboard prototypes. Testers included research divers as well as ship husbandry divers.

Triton also conducted benchtop testing of the breadboard prototypes (**Figure 1**). The test design included the full communication system path. For receive communications, a speech signal was produced by a speaker in front of the Amcom III surface unit and recorded at the ears of a G.R.A.S. KEMAR 45BC-1 head and torso simulator (HATS).

For transmit communications, a speech signal was generated by the HATS mouth and recorded by a G.R.A.S. 46AF calibrated microphone in front of the surface unit (**Figure 1**). A series of Harvard Sentences were recorded as speech signals by Triton engineers to allow for reproducible speech in varying scenarios.

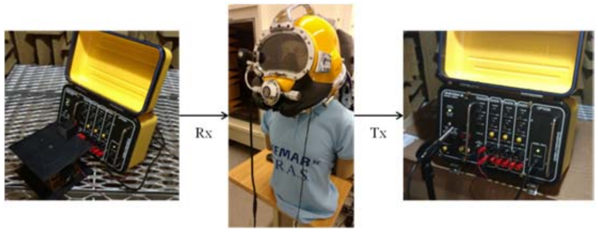

Fig.1. Triton Test Setup

The breadboard prototypes were also tested in-water. An NSMRL diver tested the system's capability up to 10 ft (4.45 psi), while the Triton team tested up to 45 ft (20 psi) for 45 minutes. A submerged test was conducted in a hyperbaric chamber up to 60 ft (27 psi).

In Phase II, Triton will conduct both formative and summative testing in a hyperbaric chamber. This testing will be followed by additional relevant environment testing at a Navy diving location, for example NSMRL, Norfolk, VA, and the Naval Experimental Dive Unit (NEDU) in Panama City, FL.

Results

By replacing the legacy transducers with new, improved transducers, Triton was able to show significant improvement in intelligibility.

Triton's communication system provides:

- Dramatically improved receive communication intelligibility (more than double)
- Improved transmit communication intelligibility
- Gas density compensation through advanced DSP
- Reduced diver noise exposure
- Operation with existing umbilicals and any dive helmet
- Increased robustness
- A drop in replacement of in-helmet comms - lower replacement cost than other options

Notes:

DIVE HELMET NOISE REDUCTION

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Background

Helmeted divers are exposed to high levels of noise. The sources of these noises can be self-generated (e.g., airflow through the demand-regulators during inhalation and bubble noise during exhalation), as well as transmitted through the helmet from underwater tools. While administrative controls (i.e., noise exposure guidance and regulations) are a necessary part of an overall hearing protection strategy, the critical component that determines success depends on our ability to eliminate the effects of various noise sources. Dive communications systems are vital to diver safety and performance but can contribute to unwanted noise.

Protection of warfighter hearing is vital to warfighter performance and reduction of long-term disabilities. Reduction of generated noise reduces the required volumes for communications. Improvement the communications system reduces overall noise exposure and improves performance.

Objectives

The main objectives of the current efforts are to 1) develop technologies to reduce diver helmet noise produced by and transmitted through dive helmets to less than 85 dB with appropriate consideration to diver's communication needs; and 2) improve diver communications at working depths while reducing diver noise, improving diver intelligibility, and increasing system reliability. Toward these objectives, the team will identify dominant sources of noise in dive helmets and develop technologies to reduce the production of noise at the source and transmission to the diver. Prototypes will be developed and delivered for testing to Naval Submarine Medical Research Laboratory (NSMRL) and the Navy Experimental Dive Unit (NEDU). An improved communications system will be developed to improve intelligibility while reducing the overall volume level for the diver and topside stations and improving system reliability.

Methods

Sources of noise were investigated through available literature, multiple Navy diver interviews and dive helmet testing. Solutions to reduce noise generation at the sources were then developed based on noise production mechanisms. Prototype solutions were designed and rapid prototyped using additive manufacturing for rapid development and test cycles. A work of breathing test setup was developed for rapid characterization of prototypes.

Fig.1. Dive helmet featuring Oceanit's Q-Dive quiet dive helmet technologies. Quiet secondary regulator and quiet free-flow air train retrofit into existing helmets and reduce diver noise exposure while enabling lower communications volumes.

The existing state-of-the-art of diver communications systems was investigated. Oceanit's approach was to first gather information from users on dive communications issues. This included interviewing commercial divers as well as Navy divers and dive technicians from mobile and non-mobile units. This information, as well as information from the solicitation, the Office of Naval Research and open literature, forms the basis for what is lacking, what needs to be improved, and what new features could be developed.

Results

Dominant sources of noise were identified to be the secondary regulator, the free-flow air train and high communication volumes necessary to hear over other noise. An advanced quiet secondary regulator prototype was developed and demonstrated 28 dB noise reduction, producing only 67 dB at 1.2 CFM. A quiet free-flow air train prototype was developed and demonstrated 14 dB in noise reduction, producing only 74 dB at 8 CFM. A work-of-breathing characterization system was developed. Improvements to work-of-breathing were developed to improve regulator performance.

Vocal communication between divers and topside tenders is challenging for several reasons:
• the combination of electronics and a wet and saline environment
• the physical limitations imposed by the dive helmet system which must provide life support and protection without unduly restricting diver movement
• the presence of electronic and acoustic noise (including feedback) which reduces speech intelligibility
• the use of Helium which affects vocalization of divers.
Prototype improvements to current dive communications systems were developed including: signal processing algorithms to reduce or eliminate unwanted sounds and acoustic effects, improvements to the dive helmet to reduce adverse effects on communications system, and improved hardware. In next phase, advanced prototypes will be developed and tested.

Notes:

A high-throughput screen identifies small molecules that protect against cisplatin- and noise-induced hearing loss

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Abstract

Hearing loss due to chemotherapy, noise and aging affects nearly 10% world population but there are no FDA approved drugs for its prevention and treatment. To address this need, we screened a library of 4,359 small bioactive molecules using a cochlear cell line and identified 10 compounds that protected against cisplatin-induced outer hair cell damage in mouse cochlear explants. The top three hits had a common cellular target; cochlear explants isolated from mice deficient in this molecular target displayed enhanced resistance to cisplatin toxicity. We demonstrated in adult mice that local delivery (transtympanic injection) of the top compound, SJZuo-4, offered protection against cisplatin- and noise-induced hearing loss. Pharmacokinetics studies showed that SJZuo-4 was effective within the inner ear fluid within approximately 6 hrs of administration. Through cheminformatics by determination of structure-activity relationships (SAR), we identified additional analogs that were more potent than our original hits. Our studies reveal a novel molecular target in the cochlea and small molecule compounds for potential therapeutic intervention of widespread hearing loss including noise-induced hearing loss in the military personnel.

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